June 2006

Dataset Analysis and Management for Use in an Ecological Analysis on Exposures to Heavy Metal Contaminated Air and Disease Rates of Autism in the United States

David Dayya

Dataset Analysis and Management for Use in an Ecological Analysis on Exposures to Heavy Metal

Contaminated Air and Disease Rates of Autism in the United States.

David Dayya

A Thesis submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Public Health at the

University Of Connecticut

2006

APPROVAL PAGE

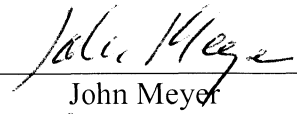
Master of Public Health Thesis

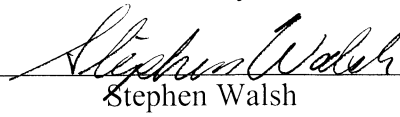
Dataset Analysis and Management for Use in an Ecological Analysis on Exposures to Heavy Metal Contaminated Air and Disease Rates of Autism in the United States.

Presented by

David Dayya

Major Advisor 
Timothy Morse

Associate Advisor 
John Meyer

Associate Advisor 
Stephen Walsh

University of Connecticut

2006

Acknowledgements

This study could not have been possible without the guidance and support of many parties including the New York City Department of Health and Mental Hygiene Division of Environmental and Occupational Disease Epidemiology and its division Director Dr. James T. Cone and his excellent staff. I would also like to thank the University Of Connecticut Faculty Community including my advisory committee Drs. Tim Morse, Stephen Walsh and John Meyer. Thank you Dr. John Graham, Atmospheric Scientist from the Northeastern States For Coordinated Air Use Management (NESCAUM), for his advice and helpfulness and Dr. Roger Lalancette Analytical Chemist, Rutgers, The State University Of N.J. Lastly, I would like to give special thanks to my Hospital Departmental Director Dr. Nelson Eng for his friendship and support throughout this endeavor and especially to my wife Lauren and my children David, Michael and Sara for their patience and understanding.

Table Of Contents

Abstract	1
Introduction and Overview	1-5
Background	6-19
Methods	19-36
Results, Tables Graphs	36-81
Discussion/Conclusion	82-89
References	90-97

Table of Figures

Figure 1 Representative EPA regions throughout the United States.

Figure 2 The number of cases reported for each school year from 1992-2003 for the 6-22 year old age bracket (lower curve) and 3-22 year old age bracket (upper curve).

Figure 3 The percent cumulative growth in the number of cases for each school year relative to the baseline year of 1992 in 6-22 year olds as compared to the growth for all disabilities for each school year relative to the baseline year of 1992 in 6-22 year olds.

Figure 4 The percent annual growth in the number of cases for each school year from 1992-2003 in 6-22 year olds as compared to the percent annual growth for all disabilities from 1992-2003.

Figure 5 Mercury Deposition Network (MDN) Monitoring Sites throughout the United States.

Figure 6 Histogram representing the frequency distribution of autism prevalence (cases/10,000 live births) in 3-22 year olds for the lower 48 states in 2003.

Figure 7 Histogram representing the frequency distribution of autism incidence (cases/10,000 live births) in 3 year olds for 2003 for 44 states (data from 4 states did not contain reported incidence).

Figure 8 Histogram representing the frequency distribution of the mean autism prevalence (cases/10,000 live births) in 3-22 year olds in 2003 for all EPA regions (derived from the collective individual state prevalence within each region (4 states did not contain reported incidence).

Figure 9 Histogram representing frequency distribution for median state prevalence (cases/10,000 live births) of autism by EPA region for 3-22 year olds in 2003 for all EPA regions
(derived from thecollective raw individual state prevalence within each region).
Figure 10 Histogram representing the frequency distribution for state mean mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.
Figure 11 Descriptive statistics and frequency distribution for state median mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.
Figure 12 Descriptive statistics and frequency distribution for state median mercury deposition concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.
Figure 13 Descriptive statistics and frequency distribution for state median mercury deposition concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.
Figure 14 Histogram representing frequency distribution for state mean mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.
Figure 15 Descriptive statistics and frequency distribution for state median mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

Figure 16 Histogram representing frequency distribution for state mean lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

Figure 17 Histogram representing frequency distribution for state median lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

Figure 18 Bar chart representing mean mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regions 5 and 6 appears to have the highest values.

Figure 19 Bar chart representing median mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 6 appears to have the highest values.

Figure 20 Bar chart representing mean mercury deposition by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 4 and 6 appear to have the highest values.

Figure 21 Bar chart representing median mercury deposition by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 6 appears to have the highest values whereas regions 5 and 9 have the lowest.

Figure 22 Bar chart representing mean PM lead concentration by EPA region for 3-22

year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 7 appears to have the highest values and region 6 the lowest.

Figure 23 Bar chart representing median PM lead concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Similar to the chart above region 7 appears to have highest values and region 6 the lowest.

Figure 24 Bar chart representing mean mercury PM concentration by EPA region for 3-22 year
olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels
from all monitoring stations within a region). Region 4 appears to have the highest values and
three the lowest.

Figure 25 Bar chart representing median mercury PM concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Again region 4 appears to have the highest value as in the previous chart whereas the other regions are much lower.

Abstract

Autism rates are on the rise across the country with many interesting theories on causation including environmental toxins such as mercury and lead (1). Datasets exist that could be used for an extensive ecological study to investigate exposures and their potential association with these rising disease rates. However often datasets are not ideal for such an analysis and need extensive modifications including cleaning and aggregating of data to make a comprehensive analysis more valid and possible. In this study the author investigates the use of three separate datasets: one for autism disease rates and the other

two representing mercury and lead levels in air. These datasets will be evaluated in relation to their methods of collection, comprehensiveness, reliability, geographic coverage and specificity, and appropriateness for a study of heavy metals and autism. A review on the subjects of mercury, lead, autism rates and the potential role of air quality is also provided. A preliminary exploratory data analysis on variables created from the datasets for use in a future ecological study was conducted using the SPSS statistical software program. This included descriptive statistics and frequency distributions for the newly created variables that represented state and regional levels were produced for and are reviewed in

this analysis. A series of tables are included representing state/regional disease rates and exposure levels that are ranked in ascending order.Abstract

Introduction

The focus of this research paper will be on the process taken in organizing and analyzing the available raw data on prevalence and incidence rates of autism, and on air exposure levels for heavy metals in the context of their potential use in an ecological study. The CDC reports the incidence of autism currently is 34/10,000 children. In terms of childhood disabilities this exceeds the rates for vision or hearing impairment, cerebral palsy, and Downs syndrome (2). The Autistic Society reports an autism prevalence of 60/10,000, which is close to 425,000 children. The annual national cost is estimated to be approximately 90 billion dollars (3). Theses numbers may seem tragic and daunting; however, they pale by comparison in estimating the true magnitude of suffering related to these diseases for these patients and their respective families.

The major objectives of this analysis will be to establish new databases that will offer the researcher an opportunity to examine trends across the country with respect to the disease rates and exposure levels of interest. I will examine three existing datasets in order to manage and reorganize the data in a way that will enable examination of the relationship between the two independent variables (mercury and lead levels in air) with that of autism rates in children throughout the United States.

The datasets will include: (a) comprehensive state autism rates collected based on federal law requiring the reporting of autism for all children in public schools under the Individuals with Disabilities and Education Act (IDEA) (2). (b) the Mercury Deposition

Network (MDN) dataset which represents wet deposition and precipitation levels of mercury concentration, and (c) the Environmental Protection Agency Air Quality Systems (EPA-AQS) dataset which contains information on particulate matter and the concentration of lead and mercury contained within particles 2.5 microns in size (4,5,6).

The question concerning environmental toxins such as heavy metals and their associations with chronic neuro-developmental diseases such as autism currently lack definitive causal understanding. This hypothesis remains a very interesting and controversial one. What makes this question even more relevant is the biological plausibility connecting these toxins through very complex biochemical reactions to many inflammatory disorders including diseases similar to those mentioned here. The free radical theory of disease is associated with numerous disease processes as evidenced by the fact that any standard textbook on the pathologic basis of disease begins with an explanation of free radical theory and their link to heavy metals (7, 8). It can be further hypothesized that not only neurological diseases, but many other diseases already have a heavy metal connection that serves as either a direct causal link or a potential contributor through the same mechanism including such common inflammatory diseases as cardiovascular disease or even the pathogenesis of cancer (7, 8). The public health controversy with respect to toxic heavy metals relates to the standard used to decide what constitutes heavy metal poisoning. Currently the standards rely on whole blood levels, and standard urine tests which may be inherently flawed as these levels are not necessarily accurate measures of other body-tissue burdens i.e. the central nervous system. It may be that blood levels are a better indicator of acute high-level toxic

exposure, whereas they do not serve as good surrogates for low-level chronic toxic heavy metal exposure or from an exposure that is now remote from the original acute insult/event. This has been evidenced most recently with the CDC's well-publicized decision to reduce the action level for lead from the original 25 to 10. However, this standard was qualified with the disclaimer that even these levels may not be inherently safe (2).

Intoxication with heavy metals such as lead and mercury share some identical symptomatology with neuro-developmental and neuro-degenerative conditions (9). Environmental toxins may be grossly under-appreciated and overlooked potential contributors to chronic illnesses, as the Healthy People 2010 report concluded (10). More research in this area is needed in order to gauge the extent of the association. It may be that one day surrogate tissue burdens/levels will replace the current standard (i.e. blood) resulting in a historic significant shift in public health policy as to how we define what constitutes toxic levels and how to accurately measure them. The current conventional methods in public health policy used in setting standards may be inherently flawed. This form of research is fundamental in its public health implications.

Heavy metal toxicity has been well known for many years. There is a theory that lead intoxication brought down the Roman Empire as a result of the lead-based drinking utensils used at the time and lead pipes. In Lewis Carroll's book Alice in Wonderland there is reference made to being as "Mad as a hatter". This adage refers to the neurobehavioral toxic effects caused by mercury and its association with the process in

felt hat manufacturing during the 19th Century. The list of historic sentinel events culminates with the incidents in Iraq and Minamata, Japan where thousands suffered the health consequences associated with acute heavy metal toxicity. In Japan an entire bay was contaminated by industrial dumping of mercury where the inhabitants relied on fish as a primary source of food, whereas in Iraq fumigants containing mercury was applied to crops of grain that was consumed by the population.(9, 11).

Mercury has known chronic effects that can be either sequelae of the acute episode of exposure or possibly the consequences of long-term exposure at low doses (9). This analysis focuses on toxicity associated not solely with the acute high level exposure but also on chronic low-level exposure through the effect of air quality via inhalation directly or indirectly through the effects of air quality on water, soil and fish contamination. By organizing our datasets into state and regional levels by year for both exposures and disease rates an ecological model can be constructed to look for potential association on a national level. An ecological study such as that suggested here would not be able to discern necessarily the immediate route of exposure that was most responsible for toxicity.

It is important to note that though this discussion has principally focused on the heavy metal controversy these issues are not unique to heavy metals. There is debate over chronic low-level exposures and long-term health effects through bioaccumulation and body tissue burdens with respect to many toxins. It involves various interest groups concerned about setting safe standards and safe levels of exposures for many toxins

including lead and mercury. This includes economic interests involving the industrial community and the government through various regulatory and advisory agencies such as the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA). Many legitimate questions have been raised around this controversy including: What standard level is the safest level of exposure over the long term? Is the level that is "safe" for me also safe for my children as well? Should the levels be set with the most vulnerable members of our society in mind, i.e. the very young and old, the immuno-compromised and childbearing-aged females? Is there enough data and research to be able to make scientifically based decisions in answering these questions? Or is a more precautionary approach warranted (12)? If there still remains doubt about what the scientific community can conclude at present should we set the most conservative and cautious standard for toxins to minimize potential unknown long-term risk or should we require definitive proof before lowering the standards any further in the interest of economics? Will these decisions affect American industry adversely and threaten jobs? The organization of these datasets for ecological study or to provide a resource for other researchers interested in this topic is a step towards clarifying our understanding of the role air toxins pose to public health.

Background

Historical Scope of the problem

Lead is ranked number two and Mercury is ranked as number 3 as the top 20 hazardous substances in the 2003 CERCLA (Comprehensive Environmental Response, Compensation and Liability Act). Here in the U.S. 158 tons of mercury were discharged in 1995, with 87% from combustion sources. A total of 714 of the 1467 National Priority List Sites identified by the EPA contain mercury (13, 14). The scope of the problem is made worse by the fact that Mercury's high volatility allows it to re-circulate in the air and deposit back to the earth where it can contaminate bodies of surface water, groundwater, and soil (14). This along with the direct contribution of the superfund toxic sites and industrial sources of discharge comprise large quantities of human derived sources of mercury in our environment (13, 14, 15). Another very significant event was the development of dental amalgams containing mercury in the 1800's. Lead contamination has largely posed a risk through lead paint in housing constructed pre-1978, and from leaded gasoline emissions deposited and collected around roads in soil, and a contributor to particulate matter in air.

Sources of Mercury and Lead

Mercury exposure to human beings is known to be from both naturally occurring sources and, more commonly, man made sources of pollution. Natural sources include volcanic activity, various mineral deposits in soil, and bacterial transformation of elemental mercury to methyl mercury. Humans have come into contact with it through mining, industrial uses, and the other sources listed below (13):

Some sources of mercury include (9)

- Alkaline batteries (leakage, production, disposal)
- Thermometers and barometers
- Grain fumigants, pesticides, and fungicides
- Tanning fabrics
- Taxidermy
- Chlorine production (as a catalyst) and polymer catalyst
- Paper pulp industry, paints
- Thimersol (a preservative in a variety of vaccines)
- thallium (the radioactive isotope used for cardiac stress testing)
- Dental amalgams
- Contaminated fish

Some sources of lead include (9)

- Batteries
- Lead alloys
- Pipes and cable sheathing
- Solder
- Paints
- Plastics
- Lead glazed ceramics
- Artistic colorants
- Cosmetics

- Munitions
- Glassware
- Jewelry
- Radioactive shielding
- Anti-knock alkyl agents in leaded gasoline
- Industrial coal emissions

Mercury and other heavy metals have been thought to have antimicrobial bactericidal properties and have even been used for medicinal purposes, i.e. Mercurochrome (a topically applied agent used to prevent infection from cuts). Dental amalgams (silver fillings) that are approximately 50% mercury have been used because of the desirable properties mercury alloys have as a dental filling material that minimizes expansion and contractions (9, 13, 16). Concerns have been raised over the possibility that there may be an association with multiple sclerosis, autism and a host of other neuro-developmental and neurodegenerative conditions (17-28).

Chemical Forms of Mercury and Lead

Mercury is found to be a liquid at room temperature and comes in various forms including inorganic mercury (Hg, Hg++, Hg+) and organic alkyl mercury (CH3Hg). Metallic mercury is a very volatile element and gives off vapors that can be readily inhaled, 75-80% of inhaled vapor is completely absorbed (14, 29). Methyl Mercury

(CH3Hg) is the principal form found in contaminated fish and is the principal form ingested. It is found in its methyl mercury form in at very high levels in a diet that includes large fish species, i.e. Tuna, Swordfish, Shark, and King Mackerel (15). Microorganisms transform elemental mercury into methyl mercury. Although seemingly a high source of natural mercury contamination, industrial waste actually contributes the elemental form of mercury, that is available for bacterial bio-transformation into methylmercury (9, 13). Air quality again provides a conduit for exposure through bacterial biotransformation into methylmercury. This type of bio-transformation is also possible in the gastrointestinal tract by the native bacteria.

Lead also shares similar chemical forms to mercury including ionic lead salts, and alkyl forms including tetraethyl and tetramethyl lead compounds.

Absorption, Distribution, Metabolism and Excretion

Elemental Mercury is absorbed more efficiently by inhalation (75-80%) than ingestion (<0.01%), Alkyl forms of mercury are absorbed through all routes, including 95% through the gastrointestinal tract. Distribution of inorganic and organic mercury includes many tissues, but primarily the brain and kidney. Mercury, especially alkyl or methyl mercury, readily crosses the blood-brain barrier. Alkyl mercury, being especially lipophilic, also is taken up by red blood cells and accumulates in brain tissue (13). Inorganic and organic mercury cross the placenta and are excreted in breast milk (13). Toxic elements are excreted primarily by the kidney. Lead shares many of the same properties in its organic alkyl form as mercury, also enabling it to cross the blood-brain barrier. Five to 10% of orally ingested lead is absorbed through the GI tract, whereas 40% or more of inhaled mercury is absorbed through the respiratory tract (11, 13, 15).

Toxicology

How do toxic heavy metals adversely affect human health? Mercury binds to sulfhydryl groups and interferes with cellular enzyme systems that can counter free radical generating pro-inflammatory reactions. Heavy metals are catalysts in free radical generating chemical reactions (7, 8, 13, 15). Free radicals such as hydroxyl (*OH), superoxide (*O2), and peroxide (H2O2) are generated and through oxidation reactions are capable of causing free radical injury to tissues (7, 8, 13, 15). Sulfhydryl containing compounds, such as reduced glutathione (GSH), can either block the initiation of free

radical formation or inactivate/scavenge free radicals. The result of this redox type reaction is oxidized glutathione (GSSG). This results in deactivation of glutathione, hence allowing generation of unchecked potentially highly reactive tissue damaging free radicals. Lead represents a catalyzing agent that increases the number of free radicals through these reactions. Hence both lead and mercury act synergistically in both increasing these reactions and inactivating antioxidants such as glutathione that keep these reactions in check, preventing them from deactivating free radical chemical species. (7, 8, 13, 15). (See reactions below).

$O2 \rightarrow {}^*O2^-$

${}^*O2^- + {}^*O2^- + 2H^+ \rightarrow H2O2 + O2$

$H2O \rightarrow {}^*H + {}^*OH$

Fe^{++} or Pb^{++} + $H2O2 \rightarrow Fe^{+++}$ or Pb^{+++} *OH + OH^-

$H2O2 + O2^- \rightarrow {}^*OH + OH^- + O2$

The action of the sulfhydryl containing glutathione in neutralization of free radicals:

$02\ H2O2 \rightarrow O2 + 2\ H2O$

$2\ OH + 2\ GSH$ (inhibited by binding with Hg) $\rightarrow 2\ H2O + GSSG$

$H2O2 + 2\ GSH$ (inhibited by binding with Hg) $\rightarrow 2\ H2O + GSSG$

Free radicals are the mediators of inflammation. Inflammation is the process by which immune cells damage invading organisms as a means of defense. However, taken to the extreme, these inflammatory reactions can also damage native tissues through the same process. Many categories of diseases are known to be linked by this common mechanism of injury, including DNA damage that can lead to cancer, autoimmune disease,

cardiovascular disease, and neuro-degenerative and neuro-developmental diseases. Free radical injury and inflammation are tied to all of these disease processes and at present, interestingly, the causes of many of the diseases mentioned here are not definitively known. Toxic elements have been known to cause cancer, and are known neurotoxins capable of producing signs and symptoms similar to those seen in neuro-developmental and neuro-degenerative diseases (7, 8, 9). This has led to the hypothesis that heavy metals may in fact have a greater causal role in these categories of disease than is currently appreciated (17-25). Concerns have been raised with respect to childhood neurobehavioral and neurodevelopmental conditions (i.e. autism, ADHD, bipolar disease, OCD) and their possible association with neurotoxic heavy metals. This concern has even led to removal of Thimersol from vaccines based on biological plausibility. Public outcry and concern of members in the medical community contributed greatly to this move (13, 15, 26-28), despite the lack of evidence for a clear definitive causal relationship.

Clinical Effects (9, 13, 15, 30)

Inorganic mercury is associated with the following:

- Gastrointestinal complaints
- Acute respiratory distress
- Tremor,
- Erethism (shyness, emotional lability/irritablity, personality change/withdrawal),
- Proteinuria
- Renal failure
- Anxiety
- Hallucinations
- Dementia
- Salivation
- Gingivitis
- Dental erosions

Organic mercury (9) (alkyl mercury compounds) is associated with the following:

- Mental disturbances
- Gingivitis
- Ataxia
- Spasticity
- Paresthesia
- Visual and auditory disturbances
- Intellectual impairment

- Tremor
- Muscular Rigidity and spasticity
- Exaggerated deep tendon reflexes
- Behavioral changes
- Skin rashes
- Cerebral Palsy

Inorganic Lead (9) is associated with the following:

Acute effects

- Abdominal pain-colic
- Encephalopathy
- Hemolysis
- Acute Renal Failure

Chronic effects

- Fatigue
- Asthenia
- Arthralgias/Myalgias
- Hypertension
- Anemia
- Peripheral Neuropathy-motor
- Neurobehavioral disturbances and chronic encephalopathy
- Impaired fertility

- Gout
- Chronic Renal failure

Alkyl Organic Lead (9) is associated with the following:

- Fatigue
- Lassitude
- Headache
- Nausea/Vomiting
- Neuro-psychiatric complaints (memory loss, impaired concentration)
- Delerium
- Seizures
- Coma

It is important to reiterate that these chronic effects can present as sequelae of acute exposures or due to chronic exposures. The critical question revolves around what is the minimal low-level chronic exposure, and over what length of exposure creates a risk of adverse health consequences.

Diagnostic Testing

Mercury and lead may be detected in numerous tissues. Although acute exposures to mercury can readily yield high blood levels (>40 – 50mcg/L) and urine levels (>10mcg/L), levels can also be detected in hair, nail and post provocation urine specimens. The longer the hair specimen obtained the more distant or long term the time

period assayed for toxic elemental exposure (11, 13, 25, 31, 32). It is also possible to give an individual a provocation challenge dose of a chelating agent such as DMPS (Dimaval) (Dimercaptopropane-1-sulfonate) or Succimer (Chemet) (2, 3-mesoDimercaptosuccinic Acid) and collect urine over a specified period of time (11, 13, 25, 31, 32, 33). The chelating agent will bind to and often draw mercury from the tissues into the blood stream where it can be excreted in the urine. Before and after urine specimens will often show an increase in mercury excretion after provocation with a chelating agent (11, 13, 25, 31, 32, 33). This may include individuals not suspected of being mercury intoxicated. As a means of diagnostic testing in suspected cases, peripheral tissue levels of mercury may be more useful than serum or urine levels, as these may serve a better role as surrogate indirect measures of total body tissue burdens or bioaccumulation. Definitive action threshold levels for these peripheral tissues (i.e. hair, nails, red blood cell, and post provocation urine levels) have not been established or uniformly adopted by laboratories, agencies and the medical community in the same way that serum blood levels or unprovoked urine levels have been accepted. Blood and unprovoked urine levels are generally better measures of acute intoxication, but as yet there are no standards for the surrogate tissue measures discussed above. The correlation between blood and urine levels and clinical toxicity can also be imprecise and therefore these conventional tests have been open to question. The average half-life of inorganic mercury is 60 days (70 days for alkyl mercury), which results in slow elimination (9). This long half-life can take over 1 year to reduce mercury levels below 5%. In the case of lead the half life is estimated to be 5-10 years (9). These facts help to explain some of the discrepancy between blood, post-provocation urine levels and clinical effects. The highest potential

sources of mercury exposure that are found in the body include dental amalgams, which may contribute anywhere from 0-70% of the total body burden of mercury and can release approximately 3-17 mcg/day, and fish consumption (11, 13, 15, 34). In the environment, source reduction and "end of pipe" measures, especially from combustion sources such as fossil fuels, would help reduce the 85% of mercury emissions released into our environment, and which are the principle source contributing to higher levels of mercury and other heavy metals in the air (14).

Mercury and Lead Standards

Currently statutory limits attempt to minimize cases of acute heavy metal poisoning, and are likely to be effective in this regard. However, there are concerns related to toxicity from chronic low level exposure and bioaccumulation (including total body tissue burdens). This is compounded by the fact that the methods used to generate risk assessments are felt to be inherently flawed in this capacity. These concerned groups argue that the level should be "0" or the lowest level current laboratory technology can detect. These tighter standards would be a similar to what is under consideration in the European Union under the precautionary principle proposal (12). The current U.S. standards were set based on a number of factors, principally risk assessment through epidemiological studies and animal toxicology studies using rodents (13, 15, 34). Epidemiological observational studies included primarily sentinel events like those in Iraq and Minamata, Japan, which were actually acute toxicity assessments that involved very high blood levels of these toxic heavy metals. These types of observational studies are likely to be the only types of human studies that will be available to us, as it is clearly

unethical to recruit individuals for double blinded, randomized, placebo controlled cohort trials involving low levels of toxic heavy metals inhaled or ingested over the long term. Animal studies relying on rodents with a lifespan of approximately 12 months and determining Lethal Dose 50 (LD50) (minimum level of toxin that will kill 50% of the rodent population) and Threshold Limit Values (TLV) (levels below which the risk of adverse health effect is believed to be low) are likely to be the continued standard used to estimate risk by extrapolating to humans, however flawed that standard. Researchers utilizing this method are essentially measuring acute effects of high level exposure and utilizing this data to extrapolate to lower levels and to human beings with considerably longer lifespans (9, 35, 36). The limitations many researchers face include species to species extrapolation, external validity and generalizability. Physiology is not identical between species, and it is widely known that animals don't share all diseases that humans have and vice versa. It is also true that toxins/medications may have different effects in humans than they do in animals (i.e. low dose Acetominophen (Tylenol) is lethal to cats and by a different mechanism of toxicity than in humans). These types of studies don't measure the effects of chronic low-level exposure in animals, as it would take a very large cohort of animals to generate enough power in order to see small effect sizes that may be present. Low level dose-response investigation in many cases is felt to be too expensive, too difficult, and impractical, especially when looking for small effect sizes i.e. 1:1,000,000 standard. The various health departments rely on the 1:1,000,000 standard as one consideration in setting "tolerably safe" allowable levels of exposure to toxins. This standard relies on an agency actually being able to determine that an adverse risk is likely to be seen less than one in a million times at the present standard (13, 14 15,

35, 36). Critics have raised the ethical argument over whether it is right to imply that 1:1,000,000 or (1:10,000,000) is a tolerable safe standard level, especially in that current laboratory technology is capable of detecting smaller levels of exposure than the current standard. Other industrialized countries have lessened the role of risk assessment in policy decisions (as well as the associated cost to conduct these assessments). Instead of using the risk assessment data to set the standard, it may be preferable to set the standard based upon the lowest level that laboratory technology can detect.

The principal counter-arguments to this have been concern over the impact that a very restrictive standard might have on industry and economics. Can this standard be met by states, municipalities, or private/public water companies in some areas where financial resources may be limited with respect to new lab technology for exposure level reduction? It is important to note that the same types of economic arguments have been raised over The Clean Water Act, the Clean Air Act, and amendments over the years that involved lowering standards (33). It can be asserted that the economy in the 1990's boomed higher than in recent history despite an era of unprecedented environmental regulation in the U.S. from 1970 - 1992. There is deep concern about the large effects from under-regulation (i.e. the Hudson River is expected to be polluted with Polychlorinated Biphenyls (PCB's) for generations because of the irresponsible practices of some industries). Current standards are not necessarily uniform, as some regions in the country have opted to set levels lower than others. This in part may be driven more by politics than science, or by the level of resources available that has allowed some regions to lower standards below federally capped levels. Obtaining data that will aid us further

in determining what standard is truly safe will remain a challenge with the present approach. It is hoped that datasets such as the ones analyzed in the course of this paper may assist in this endeavor. There have been efforts made to establish modeled data from raw data including datasets similar to the ones used in this analysis as well as industrial emission levels and the Toxics Release Inventory (TRI) data in order to assign risk to different regions of the country where there may not be any direct measurements.

Methods

The Datasets and Geographic Considerations

It was decided to proceed with the analysis at two levels, state and regional.

Autism Data

The first level would include using the health outcome data based on the state registry requirements to report children with autistic disorder and autistic spectrum disorders required through the Individuals with Disabilities Education Act (1). The data on autism was collected and archived for all the states by the organization Fighting Autism which eased the refinement of this dataset for the purpose of this analysis. This federal legislative act requires each state to report cases every year; however, it leaves the criteria for determining autism disability category to the individual states. Although this suggests that there will be some variability in what cases are actually reported from a given state, it should be somewhat standardized as the diagnosis will likely be deferred to the medical community. Conventionally autism and autistic spectrum disorder is diagnosed based on expert opinion including that of the primary care provider, neurological and child

psychiatric concurrent opinions. The cases usually are identified based on the DSMIVR diagnostic criteria or very similar clinical criteria for autism and autistic spectrum disorders which defines autism according to the following diagnostic criteria (3):

Autistic Spectrum Disorder, including Asperger's Syndrome

"Autism: DSM-IV indicates that the essential features of Autistic Disorder are the presence of markedly abnormal or impaired development in social interaction (e.g., use of eye-to-eye gaze, facial expression, poor peer relations, little interest in establishing friendships) and communication (e.g., may be a delay in, or total lack of the development of spoken language; there may also be the repetitive use of language) and a markedly restricted repertoire of activities and interests (e.g., there may be an encompassing preoccupation, inflexible adherence to a non-functional routine, stereotyped movements). Manifestations of autistic disorder vary greatly depending on the developmental level and chronological age of the individual. The disturbance must be manifest by delays or abnormal functioning in at least one of the following areas prior to age three years: social interaction, language as used in social communication, or symbolic or imaginary play. There is typically no period of unequivocally normal development, although one or two years of relatively normal development have been reported."

"MR may or may not be a feature of autism but for 80% of autistic children MR is present (Happe, 1994)."

"Courchesne et al. (1994) argues for a rethinking on the role of cerebellum as central to the task of coordinating attention. Courchesne found neuroanatomical evidence of loss of Purkinje cells, which form a primary component of the cerebellum. The cerebellar connections include areas such as the prefrontal and posterior parietal cortex and the reticular activating system. These researchers consider that the impairment of attention could alter social attention and the ability of the child to coordinate her attention with another person. Courchesne's research suggests strong evidence for a neocerebellar cause for autism. This work combines psychological or joint social attention, anatomical (MRI) studies and cognitive factors. Not being able (neurologically) to coordinate attention disrupts social interaction and understanding [cf. ADHD] (Sigman, 1995). The disorders most likely to accompany autism are mental retardation and epilepsy. The degree of impairment varies. Self-injurious behaviour (SIB) such as self-mutilation and head-banging also can accompany autism and may be a way of gaining attention or to provide self-stimulation so as to obliterate unwanted demands and aversive stimuli (Carr, 1977). The SCERTS model of intervention (Dawson & Osterling, 1997) addresses the core, underlying deficits in autistic children, as well as the heterogeneity amongst these children. This model of intervention also addresses the associated difficulties experienced by the social community of persons relating to these children. As new and effective models of partnering with parents of autistic children are brought forth, life for these parents becomes less overwhelmed by the intervention system involved with their autistic child."

> "Asperger's Syndrome is similar to Autism in that affected children have impaired social interactions, and restricted and stereotyped behaviours and interests. However, children with Asperger's Syndrome typically display normal intelligence, and do not show significant language delay or mutism. Their motor skills are marked by clumsiness not usually seen in the autistic child. They typically have an extensive vocabulary but tend to talk extensively about subjects of interest primarily to themselves. Their thinking tends to be concrete and they have difficulty perceiving the feelings of others."

It is readily apparent from this passage that certain higher functioning forms of autism can present diagnostic challenges, which could present as a potential filter to the reporting of cases in the database. Early intervention or "birth to three" programs established under the federal IDEA act provide a range of services to children with developmental disabilities which are yet another filter to reporting a child under the age of two. This of course assumes that a child younger than age two has received healthcare services in order to be referred into this federally funded state administered program. When a child turns three the local school board takes over from the early intervention program in order to have continuity of services which would provide yet another filter to reporting (54). Limited access to available services may restrict families from lower socioeconomic groups to early intervention services. For example, access to services could be as a result of the reduced access to health care, as the program requires a medical referral.

There have been concerns that the increased prevalence that is widely reported in autism may be related to better reporting or more diagnostic awareness on the part of clinicians. However, a review of 54 published studies showed that the increase in autism prevalence in the U.S. could not be explained by changes in diagnostic criteria or improvements in case ascertainment (55). This further supports the findings and position of the CDC, the Autism Society of America and the findings reported by Fighting Autism that this rise in prevalence is genuine (1, 2, 3). There are also competing theories on the causes of autism, among them being the genetic factor. However, usually rising prevalence is not typical of genetic diseases. Despite the suspicion of environmental neurotoxins as a cause of autism it would present a stronger argument if the underlying mechanism to the disease was known. Heavy metal neurotoxins damage tissue through either an inflammatory mechanism or through enzyme inhibition. Some studies have supported the role of inflammation in autism and the presence sulfahydryl heavy metal complexes in children's urine (56, 57, 58).

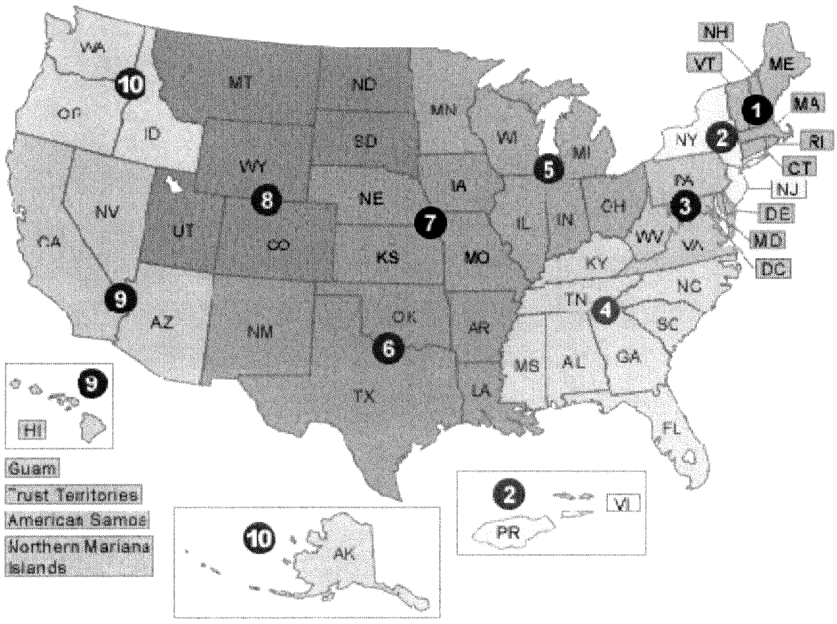
In general young children with autism are not subtle in their presentation, except perhaps in higher functioning forms of autism such as Aspergers syndrome. This makes it less likely that parents, clinicians or teachers will not notice these children, especially since they will typically present with associated developmental delays that are difficult to overlook. The activation of services, often greatly needed by these families, will generally require a medical evaluation as well. The registry provides data for a given state but it does not provide data at the county or municipal levels. Therefore it will not be possible to study regions on a scope smaller than the state level i.e. municipal or

county level. State prevalence was provided, as well as incidence by age and birth year. The incidence rates that are available were calculated by subtracting two consecutive years of reported prevalence rates for a particular age group. The incidence rates are then reported for each age group. There is apparently data missing for three and four-year old children from some of the states. This is likely due to variation in the ability to access services, or that these children are not in the school system (as pre-school and kindergarten are not universally available). This latter possibility is supported by noting that prevalence and incidence rates abruptly rise around age five, which is when children are generally required to attend school. It may be preferable to use a range of ages to represent the incidence in young children for an ecological study. This summation of the incidence for different ages would yield an overall incidence for children over a given age range that would be more restricted than the overall age range used in the state registry data (which includes 3-22 year olds). The autism dataset presents cases per 10,000 live births for both incidence and prevalence.

At the second level it was decided to assign regional levels based on the EPA's regional map (figure 1)(37). The EPA administrative regional map offers the opportunity to divide the country according to established regions rather than to create regions based on the researcher's preference. The other maps that were considered included the National Oceanic and Atmospheric Administration (NOAA) climate map and a national historical region map. The historical region map was rejected as it was felt to be less practical for the purposes of an ecological study. The NOAA climate map was rejected due to the fact that its Northeast region included states bordering the Tennessee Valley that were in areas where power plant coal combustion was more widely used. This was not felt to suit

a regional analysis that might be used to compare air quality in a region of the country with high coal combustion sources of energy to one that relied less on that source of energy. Regional level analysis could be conducted by assigning a regional mean and median prevalence from the data presented for the individual states.

Figure 1 Representative EPA regions throughout the United States.



It was felt that a regional analysis would lessen the effect of population mobility (38, 39). Another justification for utilizing a regional analysis included separation of regions of the country in order to assess exposure based upon established wind patterns. Wind patterns such as perennial wind patterns and winter jet stream present a conduit responsible for the pattern of deposition and recirculation of the various toxins. The wind patterns generally flow from West to East along either the winter jetstream or perennial wind patterns, often carrying toxins from one region of the country to another (40). This has been a major concern for certain regions of the country, including the Northeast, which has made legal challenges against states in other regions of the country that burn fossil fuels such as coal and result in poorer air quality in other regions of the country (41). Coal contains toxins including heavy metals that are carried along established wind patterns to areas that may

greater restrictions on the use of air-contaminating sources of energy (42). By exploring the exposure data on a regional level it may be possible to study the health effects on a regional scale as well.

The autism disease dataset was graphically analyzed by Fighting Autism and demonstrates an annual growth in total cases that exceeds all other disabilities. Percent cumulative growth as compared with the baseline cases from 1992, when reporting data began as required through the Individuals with Disabilities Education Act, shows consistent growth for each year. Percent annual growth is also reflective of this as both growth rates for autism exceed that of all disabilities. These consistent trends are also reflective of each state in relation to a disturbing national trend of rising rates of autism. (figures 2-4)(1, 3).The autism disease dataset demonstrates strong consistencies between states in relation to a disturbing national trend of rising rates of autism. (figures 2-4)(1, 3).

Figure 2 The number of cases reported for each school year from 1992-2003 for the 6-22 year old age bracket (lower curve) and 3-22 year old age bracket (upper curve).

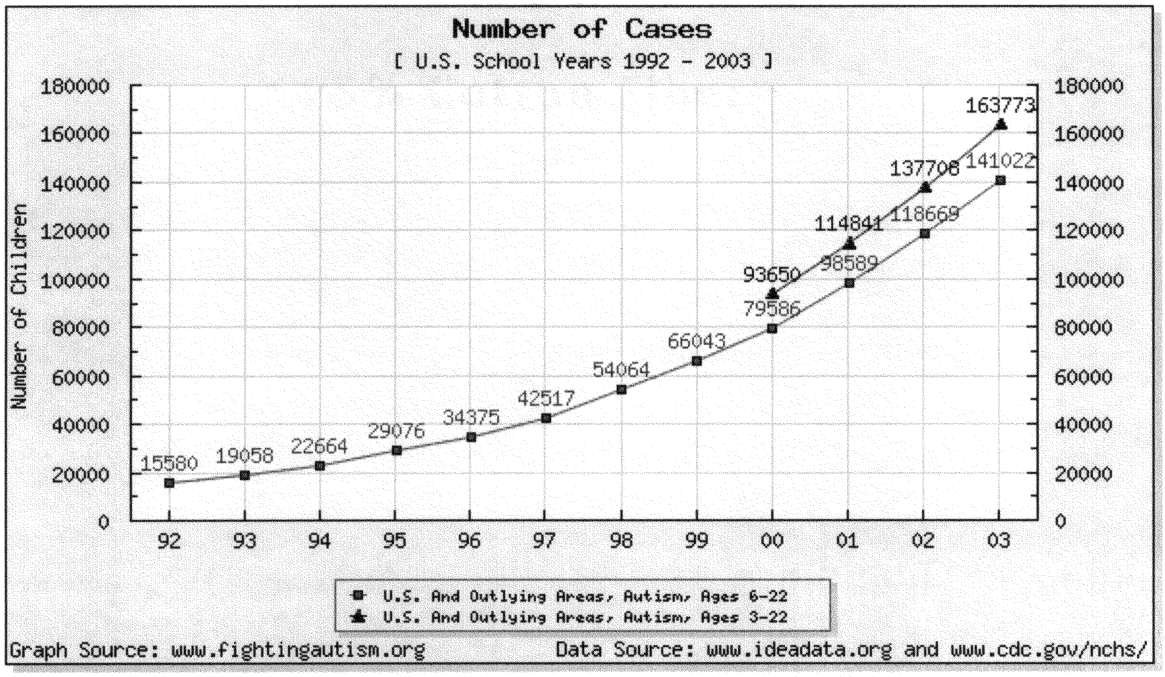


Figure 3 The percent cumulative growth in the number of cases for each school year relative to the baseline year of 1992 in 6-22 year olds as compared to the growth for all disabilities for each school year relative to the baseline year of 1992 in 6-22 year olds.

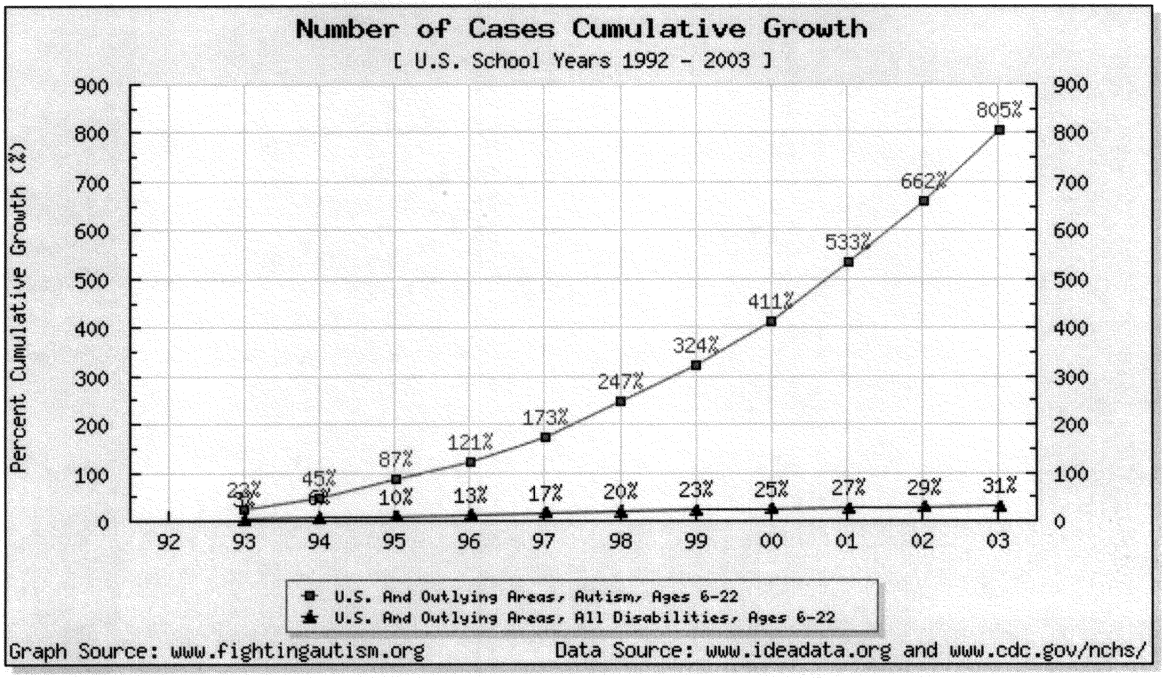
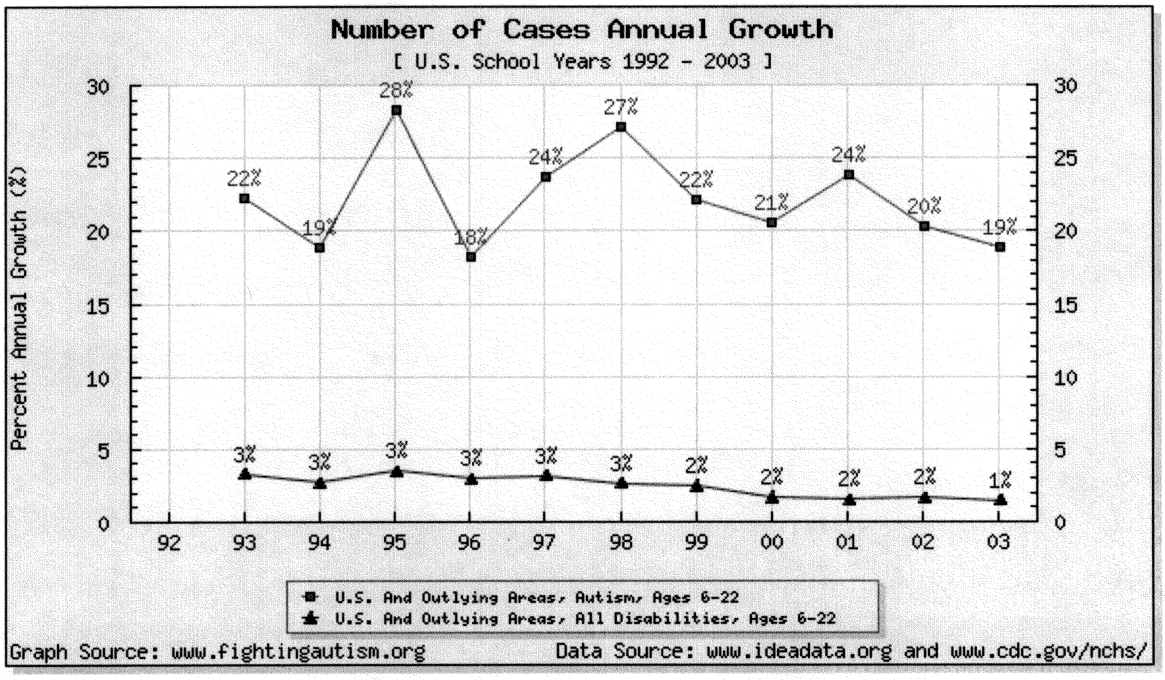


Figure 4 The percent annual growth in the number of cases for each school year from 1992-2003 in 6-22 year olds as compared to the percent annual growth for all disabilities from 1992-2003.



Exposure Datasets Overview

Mercury and lead air levels were available in the MDN and EPA-AQS databases (4, 5, 6). A thorough internet based review was used to assess the strengths and weaknesses of the various datasets. These datasets provided raw data to represent the exposure levels and were selected because they did not rely on modeling. Initially it was considered to use the EPA's National Air Toxics Assessment (NATA) dataset (43). However though this did assign values for the toxins of interest based on emissions/releases, this modeling data has been readily acknowledged by the EPA to underestimate the levels of toxins when compared to actual measurements (44). The NATA dataset reports emissions on a county by county basis for the entire country. It however does not offer direct sampling results

but instead offers modeling data based on these emissions for 1996 and 1999 (43). It then uses the model to infer risk assessment for different regions of the country. Other organizations, including the Northeastern States for Controlled Air Use Management (NESCAUM), are using modeled data to assign exposure levels for toxins that are expected to be closer to actual measurements. (45). It could be agued that using the NATA dataset, despite the conservative bias in modeling, may be reasonable as long as the bias is systematic. However, for the purposes of this analysis it was decided to limit the analysis to the raw datasets such as the Mercury Deposition Network (MDN) and the EPA Air quality Systems (AQS) datasets since it was felt that they would be closer to actual levels (4, 5, 6).

AQS Dataset

AQS provides raw data on Particulate Matter (PM) for both lead and mercury, whereas MDN uses wet deposition and precipitation concentrations as an indirect measure of air mercury levels. The EPA AQS dataset offered more direct measurements of particulate matter in the 2.5 micron range. This particulate size was felt to be especially useful as it is more likely to persist for longer periods in the atmosphere, and this could lengthen the time interval available for assay than what might be expected for larger particulate sizes. It would also potentially increase the interval of exposure as a result of this persistence in ambient air while increasing the range of environmental deposition and contamination. Also, in terms of physiological considerations, the 2.5 micron size also is known to migrate further into the respiratory system where gas exchange occurs, leading to more

absorption than larger particulate matter sizes that may be trapped in more proximal airways that do not participate in gas exchange (5, 6).

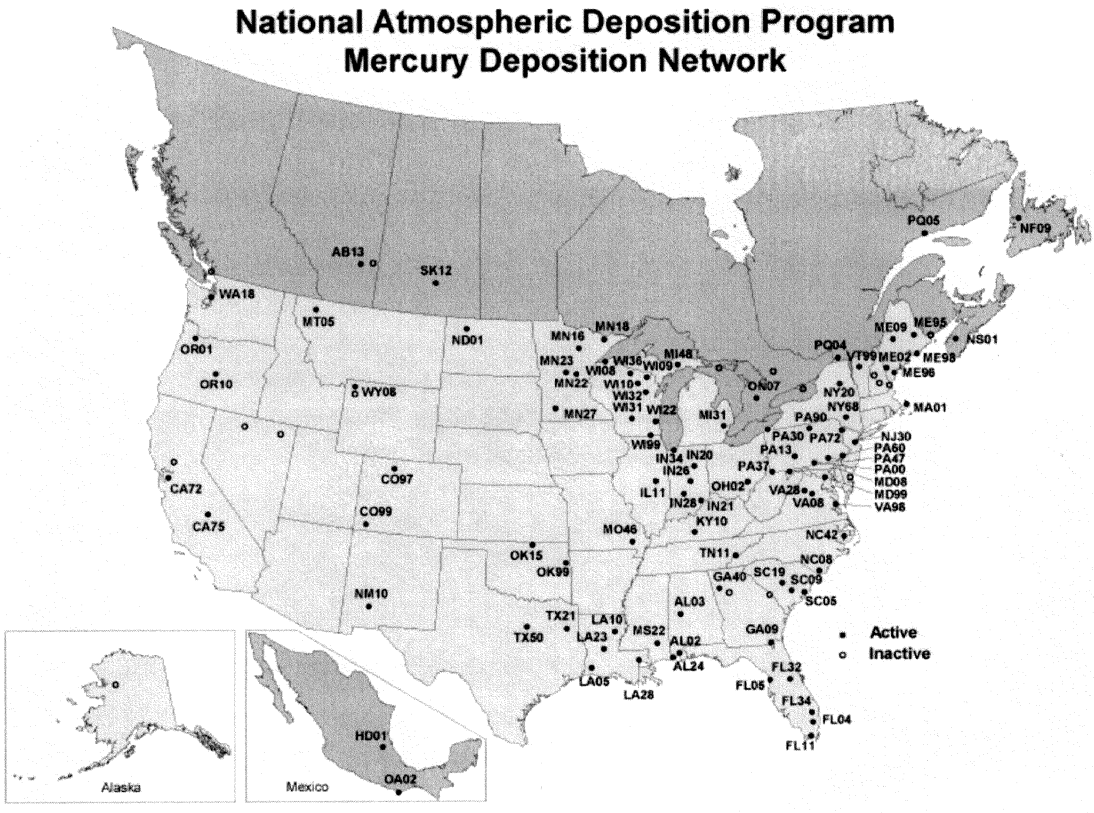
The AQS data breaks down the PM as primary or secondary generally based on size less than or greater than 2.5 microns. The larger secondary particles are contributed from sources such as roads, whereas the smaller primary particles develop in the atmosphere from sources such as power plants. It is possible to have large particles form from primary sources and have small particles form from secondary sources. For the purposes of this analysis the PM 2.5 micron was chosen and the levels for both lead and mercury were used. This allows for the inclusion of three separate indirect indicators for the level of mercury (i.e. precipitation, deposition and particulate matter levels) in the atmosphere, and one for the level of lead, which is available as part of particulate matter in the air. Precipitation and deposition levels for lead were not available. Mercury also has a vapor state and can be found in particulate matter. It is important to note that particulate matter constitutes aerosolized droplets, products of incomplete combustion such as soot and smoke and other dust particles (5).

MDN Dataset

The MDN data is derived from sampling stations that have analyzed precipitation or soil samples for concentrations of mercury in different regions of the country (see map of MDN sites below). This is known as the "wet-dep" dataset. The samples are collected over the course of the year on a biweekly basis. The mercury levels tend to be higher in the Spring to Summer months. The collection date chosen to estimate their regional

median and mean levels was consistent for all states used in the analysis. Many states had more than one station these were also collapsed into a median and mean assigned value for each respective state. This was also done for the AQS data. Both means and medians were calculated, as it could not be determined in advance whether or not outliers were important in the overall distribution of toxins. The advantage of the MDN dataset as compared with the NATA dataset was its reliance on actual deposition and precipitation concentrations as indirect measurements of mercury in air, whereas the NATA dataset uses emissions/release raw data to model the air concentration of mercury and lead (4, 5, 6).

Figure 5 Mercury Deposition Network (MDN) Monitoring Sites throughout the United States (4).



Assay Methods

The exposures were assayed by using absorption/emission spectroscopy, which is the current state of the art standard in heavy metal assay. This technology is the standard most often used whether we are assaying solids, liquids or gases. It is the same technology used whether we are assaying drinking water, blood, or air samples. The assay methods use the Beer-Lamberts law to derive concentration from a sample based on the light transmittance through the sample of interest. A beam of light is transmitted through a sample at a wavelength that is readily absorbed by the chemical species. The amount of light absorbed or the absorbance is directly proportional to the concentration of the chemical substance in the sample (4, 5, 6, 47).

Population mobility as a potential confounder

The potential confounding effect of population mobility was considered (as discussed above), but was felt to be limited because of the inclusion of a regional approach. Although Americans are considered a very mobile group of individuals, a review of the census data suggested that most of the mobility is relatively local, that is, within an individual's state or region. Also, with respect to our population of interest, these patients and their families may be more likely to need the assistance and support of extended family and friends, which may provide a further incentive to remain within the local region (38, 39).

Data Management and Aggregation of the Exposure Datasets

The data from both the AQS and MDN datasets were imported into excel spreadsheets in order to aggregate based on year and on individual states (4, 5, 6, 47). These were very complex databases. The data was presented as a textfile (.txt) and was not separated by years of interest but rather by monitoring stations and/or measurement period (i.e. biweekly in the case of the MDN dataset). The textfiles were imported into an excel spreadsheet and aggregated for the states that had data measurements available and for the respective year or years of interest. Some states had no monitoring stations, whereas others had numerous stations. This limited the number of states that could be assigned mean and median exposure levels for the separate toxins. This poses a challenge as it might justify the establishment of inclusion criteria for the states which would further limit the number of states available for analysis and decrease our sample size even further. Some states had only one monitoring station; it was decided to allow all states with any measurements to be included even those with scarce monitoring sites. Sites monitored on a continuous basis.

Another consideration was what years to include in the analysis. It was decided to use the most recent year that health outcome data was available, 2003 (1). Using the exposures from the same year would result in a cross-sectional design without a time lag to allow for the time for development of disease. This was considered because exposure data from earlier years had less abundant data than for more recent years. However, it was felt that it would be important to build temporality into a model for an ecological analysis of this

type. The lag time between exposure, diagnosis, and actual reporting of cases was assumed to range between 1-3 years. Therefore, a three year lag was chosen. Children who are identified as having autism within the first years of life usually receive services under the birth to three state programs and are likely to be reported at that time, unless the child has not received any services. An abrupt rise in reporting around age 5 was noted, which is the typical mandatory age that children begin school. Delayed diagnosis could also contribute to the underreporting, as could parental ambivalence, and varying state criteria. Therefore a three year lag with year 2000 exposure data and year 2003 disease rates were chosen. It is recognized that the exposure period may have been longer, including the prenatal period, or even have accumulated in the mother prior to conception. However, a three year lag period was considered reasonable for this analysis since it offered a good fit between the disease's natural evolution to the symptomatic phase, and took into consideration the theoretical exposure period (1, 2, 3).

Incidence could feasibly be used in a number of ways, similar to the prevalence. For example, it would have been appropriate to use the incidence in three-year old children (the intent of the three year lag). That presumes that a child becomes symptomatic and is affected at age three. Manifestations of ASD usually develop within the first year of life and may extend as far as three years. It is less common to find children initially manifesting symptoms of autism beyond age three (3). Another potential design, though more labor intensive, might be to use a range of ages for incidence such as that corresponding to a 1-3 year lag. This could permit a broader and more comprehensive and complete analysis. However, in order to allow each state to serve as its own control it

would be desirable to have include at least one other set of years with a similar lag period between exposure values and disease rates. An ecological model, for example, might use the 1997 exposure data with the 2000 autism rates in addition to the year 2000 exposure data and the year 2003 autism rates. However this would exclude preclude using the AQS PM data for mercury and lead since it only covers years 2000-2005 (5). The MDN dataset could, have been utilized as its measurements go back as far as 1996, although the number of monitoring stations and their respective measurements are limited in the earlier years (4). The data obtained for this analysis used the 2000 exposure data and the 2003 autism rates, as the interest in this analysis was to build a set of data for exploratory data analysis and provide a template to add further successive years in order to make an ecological analysis feasible.

The data could be collapsed into ordinal level data as low, moderate or high prevalence or incidence rates of disease representing the outcome variable, with independent variables likewise collapsed. This could facilitate an exploratory data analysis using rank order hypothesis testing. However the data could also be kept in its continuous scale for rank order comparison using the two periods of interest for each of the states. A third nominal scale predictor variable using region of the country could also be included to study a region of the country and its correlation with autism rates, but this may introduce multicollinearity. The data could then be hypothesis tested in a linear regression model treating all the data as interval scale variables. A regression model could also include effect modifiers and control for potential confounders such as proportion of housing pre-1978. Age of dwellings was considered an important covariate as an independent source

of lead exposure, since lead paint use was more common in older housing. This was important since lead paint is the greater source of lead exposure to children through ingestion (2).

Road density and fish consumption as covariates

Road density and proportion of fish consumption were also considered as potential confounding variables for inclusion. However it could be argued that these sources, especially fish contamination, are, to some extent, the end result of the airborne conduit and recycling of these toxins in the environment, especially in the case of mercury. Lead which has deposited along roads from the days of leaded gasoline is also a potential exposure source, along with industrial coal burning power plants. Road density was not included in the analysis as it seemed to offer only a way of discerning what was the greater contributor to air levels of lead toxin since the banning of leaded gasoline. The cycling of mercury in the environment from combustion sources is a primary source of fish contamination. The air levels are a conduit for the exposure through ingestion from this source in addition to direct discharges into water. However, as fish may not necessarily be from local sources their contamination may have occurred outside of the region of interest. An ecological analysis that could be conducted from the datasets created in this analysis would not be seeking to discern which of the primary sources of exposure was most responsible but rather looks at air quality as the conduit to many of these exposures in a more general way (2, 11, 14, 15, 29, 30, 34, 48).

For future study, an ecological analysis could be better treated in a regression model and would test mercury soil deposition level, precipitation or rainwater concentration levels and PM2.5 concentration levels in order to shed light on whether any of these somewhat redundant measures serves as a better surrogate for atmospheric levels of concentration with respect to health effects. Although multicollinearity is possible and should be suspected it could be assessed through a regression analysis. The researcher could also construct separate models to determine which model yields the more powerful results in an exploratory study.

Results

All autism disease rates were obtained from the U.S. Department of Special Education and collected as part of the IDEA act and acquired through Fighting Autism. The exposure data was obtained from MDN, EPA-AQS. The mean and median values for mercury deposition concentrations are calculated by including all the values obtained from all the monitoring stations throughout the entire year to produce a representative mean and median value for each respective state and EPA region. The identical process is used to obtain a representative mean and median value for the PM data from the EPA-AQS dataset.

The SPSS statistical software application was used to analyze and study the data. Descriptive statistics and frequency distributions were obtained for the numerous variables created for an ecological study from the datasets. Median and mean values were

created to represent each state and each of the EPA regions. EPA regions 1 and 2 were merged to better represent the Northeast, as Region 2 included only two states, New Jersey and New York. Incidence of autism in 3 year olds for 2003 for all available states was also included. The disease prevalence for autism was taken from the state data and combined by region. However, exposure levels are not presented by region in the results section, but rather are represented by the state levels and are used to generate mean and median exposure levels. Regional exposure levels were created in the data management process for later analysis in an ecological study.

Please refer to the ranking tables at the end of the results section while reviewing the tables and graphs as states and regions are displayed.

All missing values coded as -9 or -999 for the exposure datasets were dropped, and the values for disease rate that were not reported were also dropped. Numerous "0" values were present despite the fact that data was reported to the fourth decimal place in the exposure datasets and were not dropped as they were presumed to represent levels that were below laboratory detection. A thorough review of the coding system did not provide a definitive answer on the solitary "0" values. Autism Prevalence is reported in (number of cases)/ (10,000 live births). Mercury concentration is reported in units of ng/L whereas mercury deposition in soil is reported as ng/m2. Mercury and Lead particulate matter are reported as mcg/m3 (Refer to the tables and figures below for further discussion) (4, 5, 6, 49).

Table 1 and **figure 6** present the data for the autism prevalence in the lower 48 states of the continental United States. Alaska and Hawaii were excluded. A fairly normally distributed but wide distribution is observed, likely due to variation in reporting. The distribution is very slightly skewed to the right. There was a mean of 40.38 cases of autism per 10,000 live births, with a median of 37.5, and a range from 14-88 by state. The largest number of states were in the 30-40 and 40-50 range (12 states each).

Table 1 Descriptive statistics and frequency distribution for prevalence of autism (cases/10,000 live births) in 3-22 year olds in 2003 for the lower 48 states in 2003.

N	Valid	48
	Missing	0
Mean		40.38
Median		37.50
Mode		29
Std. Deviation		15.392
Variance		236.920
Skewness		1.099
Std. Error of Skewness		.343
Kurtosis		1.853
Std. Error of Kurtosis		.674
Range		74
Minimum		14
Maximum		88

Figure 6 Histogram representing the frequency distribution of autism prevalence (cases/10,000 live births) in 3-22 year olds for the lower 48 states in 2003.

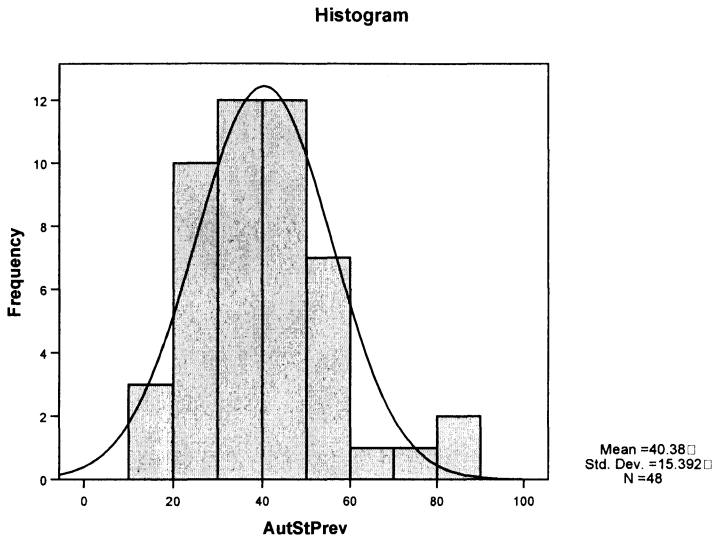


Table 2 and figure 7 present the data for the autism incidence rates for 3 year olds in 44 states out of 48 states in the continental United States. The incidence rates for four states were not available including Arizona, New Jersey, New York, and West Virginia. A wide distribution is observed that is skewed to the right and is likely due to under-reporting in the younger age groups. There was a mean of 12.28 cases of autism per 10,000 live births, with a median of 9.70, and a range from 2-38.7 by state. The largest number of states were in the 5-15 range (approximately 32 states).

Table 2 and figure 7 present the data for the autism incidence rates for 3 year olds in 44 states out of 48 states in the continental United States. The incidence rates for four states were not available including Arizona, New Jersey, New York, and West Virginia. A wide distribution is observed that is skewed to the right and is likely due to under-reporting in the younger age groups. There was a mean of 12.28 cases of autism per 10,000 live births, with a median of 9.70, and a range from 2-38.7 by state. The largest number of states were in the 5-15 range (approximately 32 states).

Table 2 Descriptive statistics and frequency distribution for state incidence rates of autism in 3 year olds representing 44 of the lower 48 states in 2003 (incidence was not available in four states).

N	Valid	44
	Missing	4
Mean		12.2841
Median		9.7000
Mode		2.10(a)
Std. Deviation		9.09375
Variance		82.696
Skewness		1.262
Std. Error of Skewness		.357
Kurtosis		1.104
Std. Error of Kurtosis		.702
Range		36.70
Minimum		2.00
Maximum		38.70

a Multiple modes exist. The smallest value is shown

Figure 7 Histogram representing the frequency distribution of autism incidence (cases/10,000 live births) in 3 year olds for 2003 for 44 states (data from 4 states did not contain reported incidence).

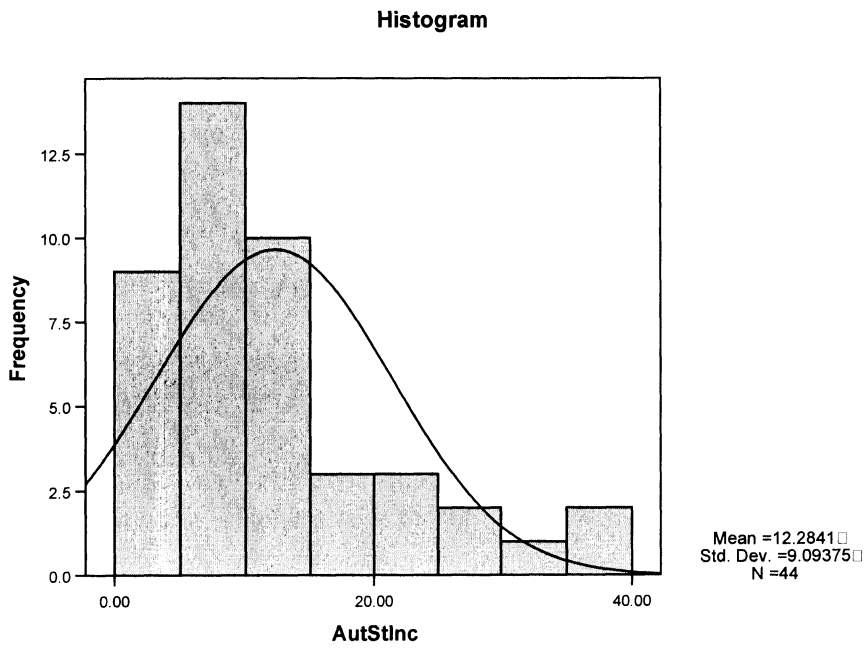


Table 3 and figure 8 present the data for the autism mean prevalence in the 9 EPA regions of the continental United States. There was a mean of 41.21 cases of autism per 10,000 live births, with a median of 42.33, and a range from 27.40-56.33 by region. The regions with the highest rates were region 1, 5 and 10. Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest

Table 3 Descriptive statistics and bar chart for mean prevalence (cases/10,000 live births) of autism by EPA region in 3-22 year olds in 2003 for all EPA regions (derived from the collective raw individual state prevalence within each region).

N	Valid	9
	Missing	0
Mean		41.2074
Median		42.3333
Mode		27.40(a)
Std. Deviation		11.7552
		0
Variance		138.185
Skewness		.054
Std. Error of Skewness		.717
Kurtosis		-2.034
Std. Error of Kurtosis		1.400
Range		28.93
Minimum		27.40
Maximum		56.33

a Multiple modes exist. The smallest value is shown

Regions 1, 5 and 10 are among the highest for mean autism prevalence by region.

Figure 8 Bar chart representing the mean autism prevalence (cases/10,000 live births) in 3-22 year olds in 2003 for each EPA regions (derived from the collective individual state prevalence within each region (4 states did not contain reported incidence). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

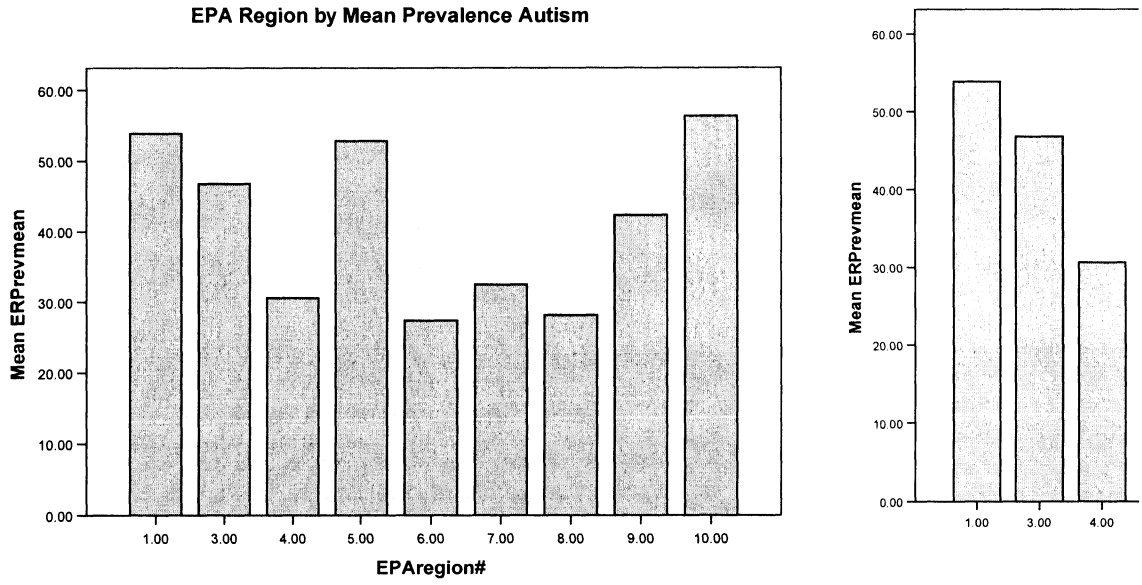


Table 4 and **figure 9** present the data for the median autism prevalence (cases/10,000 live births) in 3-22 year olds for the EPA regions of the continental United States. There was a mean of 38.94 cases of autism per 10,000 live births, with a median of 44.00, and a range from 27-52 between regions. The regions with the highest rates were (1, 5, and 10).

Table 4 Descriptive statistics and bar chart for median prevalence (cases/10,000 live births) of autism by EPA region for 3-22 year olds in 2003 for all EPA regions (derived from the collective raw individual prevalence from each state in that region).

N	Valid	9
	Missing	0
Mean		38.9444
Median		44.0000
Mode		30.50(a)
Std. Deviation		9.57681
Variance		91.715
Skewness		-.057
Std. Error of Skewness		.717
Kurtosis		-2.013
Std. Error of Kurtosis		1.400
Range		25.00
Minimum		27.00
Maximum		52.00

a Multiple modes exist. The smallest value is shown

Figure 9 Bar chart representing median state prevalence (cases/10,000 live births) of autism by EPA region for 3-22 year olds in 2003 for all EPA regions (derived from the collective raw individual state prevalence within each region). The highest prevalence regions include 1, 3, 5, and 5. Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

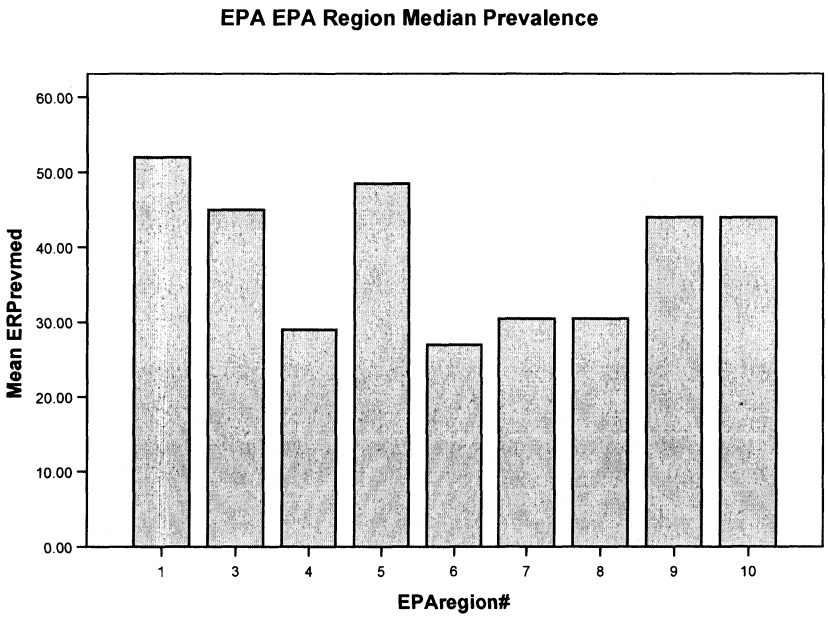


Table 5 and figure 10 present the data for mean mercury concentration in precipitation for the 20 states with monitoring stations that report to the MDN. A wider range is observed that is skewed to the right and suggests the presence of outliers, including New Mexico

(30.20 ng/L) and Wisconsin (35.80 ng/L). The "0" values in the data are probably responsible for the skewed distributions. This could possibly be explained by fewer 0 values in these states, however this should be explored further. The mean was 4.99 ng/L and the median was 13.60 ng/L and a range of 7.86-35.80.

Table 5 Descriptive statistics and frequency distribution for state mean mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

N	Valid	20
	Missing	28
Mean		14.9894 45
Median		13.6049 00
Mode		7.8606(a)
Std. Deviation		7.00205 63
Variance		49.029
Skewness		1.969
Std. Error of Skewness		.512
Kurtosis		4.000
Std. Error of Kurtosis		.992
Range		27.9395
Minimum		7.8606
Maximum		35.8001

a Multiple modes exist. The smallest value is shown

Figure 10 Histogram representing the frequency distribution for state mean mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

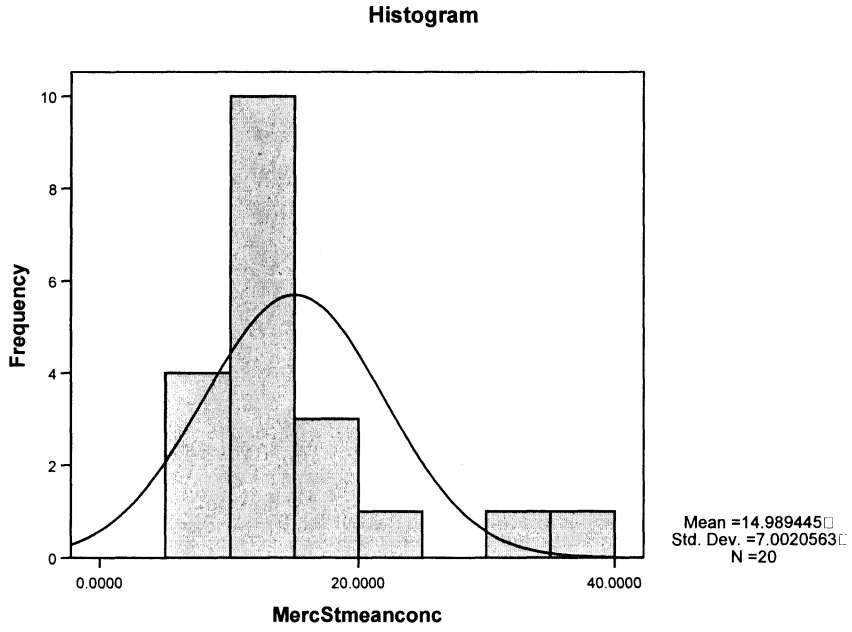


Table 6 and **figure 11** present the data for median mercury concentration in precipitation for the 20 states with monitoring stations that report to the MDN. A wide range is observed that is skewed to the right and suggests the presence of outliers. The "0" values in the data are probably responsible for the skewed distributions with a solitary outlier New Mexico. There was a mean of 10.89 ng/L, with a median of 10.52 ng/L, and a range from 5.44-27.33 by state. The largest number of states were in the 5-17.5 range (20 states).

Table 6 Descriptive statistics and frequency distribution for state median mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

N	Valid	20
	Missing	28
Mean		10.894750
Median		10.515000
Mode		5.4400(a)
Std. Deviation		4.8196409
Variance		23.229
Skewness		2.087
Std. Error of Skewness		.512
Kurtosis		6.702
Std. Error of Kurtosis		.992
Range		21.8900
Minimum		5.4400
Maximum		27.3300

a Multiple modes exist. The smallest value is shown

Figure 11 Descriptive statistics and frequency distribution for state median mercury precipitation concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

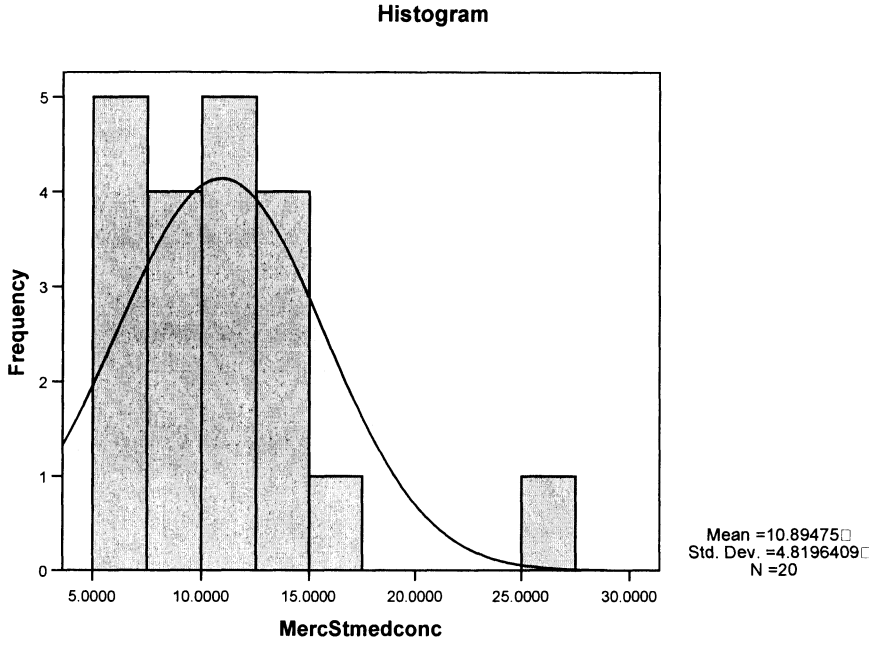


Table 7 and **figure 12** present the data for mean mercury deposition in soil for the 20 states with monitoring stations that report to the MDN. There was a mean of 245.05ng/m2, with a median of 248.58ng/m2, and a range from 96.11-436.58 by state. The largest number of states were in the 150-350 range (16 states). A wide range is observed that appears normally distributed. This differs from the mean and median mercury concentrations that were more skewed, and this could reflect that soil may better reflect a longer duration of bioaccumulated levels which are less likely influenced by factors that effect the concentration in rainwater (such as the amount of rain and the

temperature). Studying the variation in levels of mercury in precipitation as compared with deposition over time would help to support this hypothesis.

Table 7 Descriptive statistics and frequency distribution for state mean mercury deposition concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

N	Valid	20
	Missing	28
Mean		245.049210
Median		248.584050
Mode		96.1133(a)
Std. Deviation		85.1595661
Variance		7252.152
Skewness		.411
Std. Error of Skewness		.512
Kurtosis		.150
Std. Error of Kurtosis		.992
Range		340.3397
Minimum		96.1133
Maximum		436.4530

a Multiple modes exist. The smallest value is shown

Figure 12 Descriptive statistics and frequency distribution for state mean mercury deposition concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

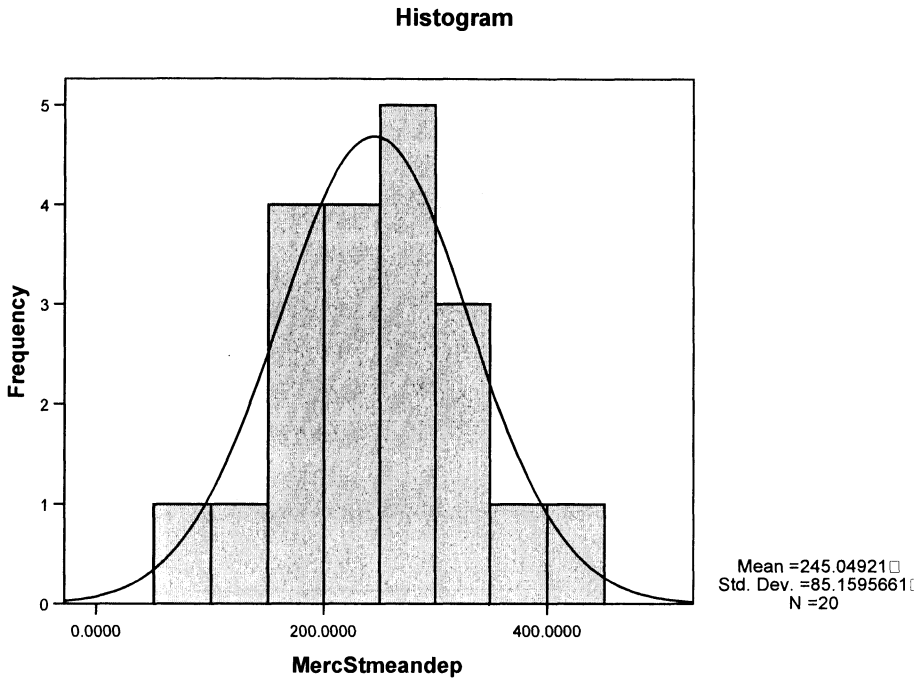


Table 8 and **figure 13** present the data for median mercury deposition in soil for the 20 states with monitoring stations that report to the MDN. A wide range is observed that appears slightly skewed to the right with one outlier value (Texas). There was a mean of 158.86 ng/m2, with a median of 144.92 ng/m2, and a range from 82.48-322.77 by state. The largest number of states were in the 50-250 range (19 states).

Table 8 Descriptive statistics and frequency distribution for state median mercury deposition concentration in 2000 for the 20 states containing monitoring stations and reporting that are reporting data to MDN.

N	Valid	20
	Missing	28
Mean		158.856500
Median		144.915000
Mode		82.4800(a)
Std. Deviation		60.8184758
Variance		3698.887
Skewness		1.030
Std. Error of Skewness		.512
Kurtosis		1.167
Std. Error of Kurtosis		.992
Range		240.2900
Minimum		82.4800
Maximum		322.7700

a Multiple modes exist. The smallest value is shown

Figure 13 Descriptive statistics and frequency distribution for state median mercury deposition concentration in 2000 for the 20 states containing monitoring stations that are reporting data to MDN.

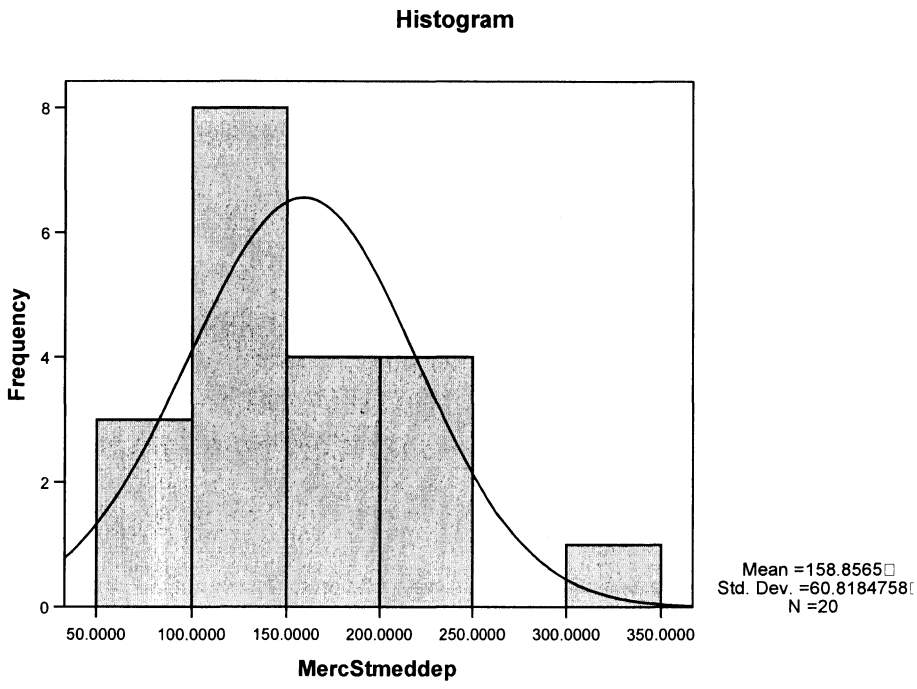


Table 9 and **figure 14** present the data for mercury state mean concentration in PM for the 18 states with monitoring stations that report to the EPA-AQS. A small absolute range of values is observed that appears skewed to the right with one outlier value (Ohio). There was a mean of 0.00098 mcg/m3, with a median of 0.00075 mcg/m3, and a range from 0.0000-0.0043 by state. The largest number of states were in the 0.0000-0015 range (16 states).

Table 9 Descriptive statistics and frequency distribution for state mean mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

N	Valid	18
	Missing	30
Mean		.000976
Median		.000746
Mode		.0000(a)
Std. Deviation		.000951 9
Variance		.000
Skewness		2.760
Std. Error of Skewness		.536
Kurtosis		8.712
Std. Error of Kurtosis		1.038
Range		.0043
Minimum		.0000
Maximum		.0043

a Multiple modes exist. The smallest value is shown

Figure 14 Histogram representing frequency distribution for state mean mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

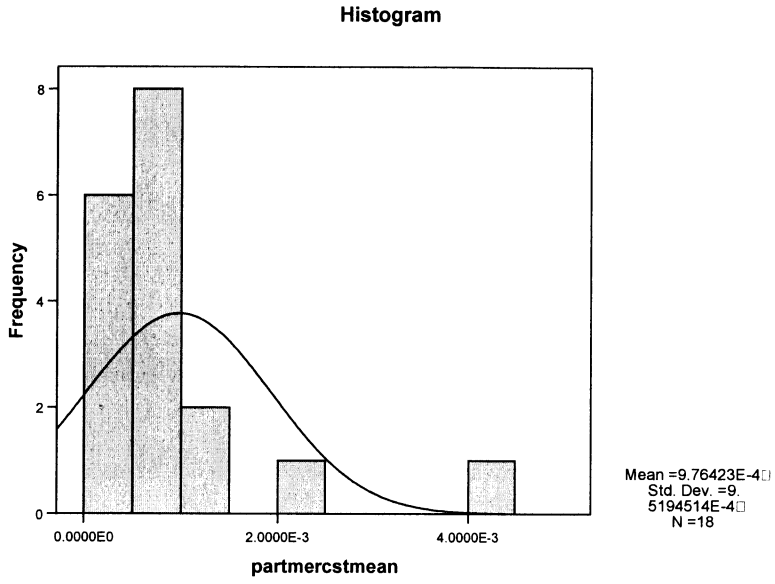


Table 10 and **figure 15** present the data for mercury state median concentration in PM for the 18 states with monitoring stations that report to the EPA-AQS. A small absolute range of values is observed that appears skewed to the right with two outlier values, Wisconsin and Ohio. There was a mean of 0.00057 , with a median of 0.00012, and a range from 0.0000-0.0043 by state. The largest number of states were in the 0.0000-0.0010 range (16 states).

Table 10 Descriptive statistics and frequency distribution for state median mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

N	Valid	18
	Missing	30
Mean		.000567
Median		.000115
Mode		.0000
Std. Deviation		.001141
		1
Variance		.000
Skewness		2.712
Std. Error of Skewness		.536
Kurtosis		6.994
Std. Error of Kurtosis		1.038
Range		.0043
Minimum		.0000
Maximum		.0043

Figure 15 Descriptive statistics and frequency distribution for state median mercury particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

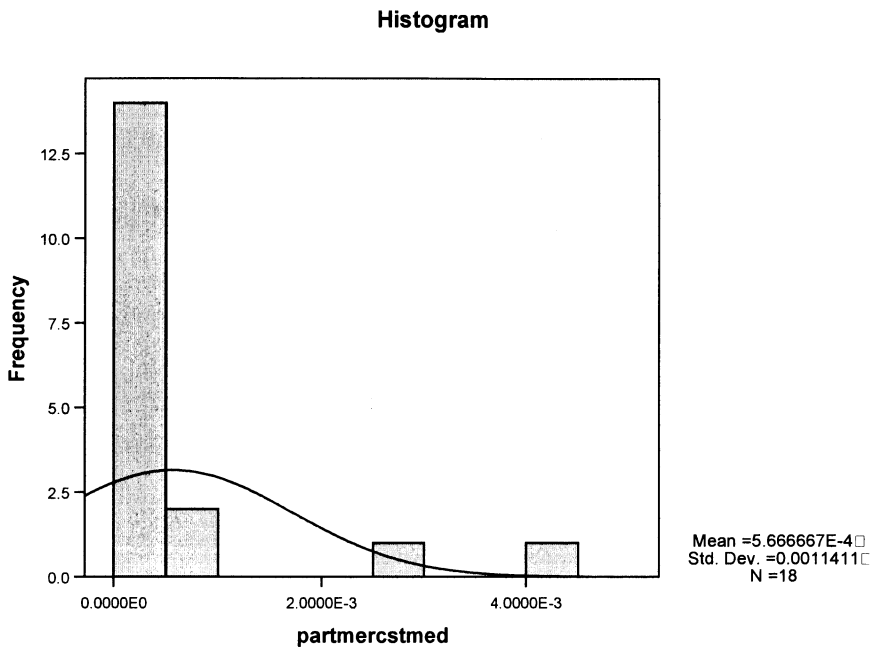


Table 11 and figure 16 present the data for lead state mean concentration in PM for the 18 states with monitoring stations that report to the EPA-AQS. A small absolute range of values that is more widely distributed than was observed with mercury PM is present that appears skewed to the right. There was a mean of 0.0072, with a median of 0.0050, and a range from 0.0027-0.0050 by state. The largest number of states were in the 0.0027-0.0100 range (14 states). This suggests greater variability in PM levels of lead than for mercury.states). This suggests greater variability in PM levels of lead than for mercury.

Table 11 Descriptive statistics and frequency distribution for state mean lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

N	Valid	17
	Missing	31
Mean		.007159
Median		.005994
Mode		.0027(a)
Std. Deviation		.003661 5
Variance		.000
Skewness		1.192
Std. Error of Skewness		.550
Kurtosis		1.097
Std. Error of Kurtosis		1.063
Range		.0134
Minimum		.0027
Maximum		.0161

a Multiple modes exist. The smallest value is shown

Figure 16 Histogram representing frequency distribution for state mean lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

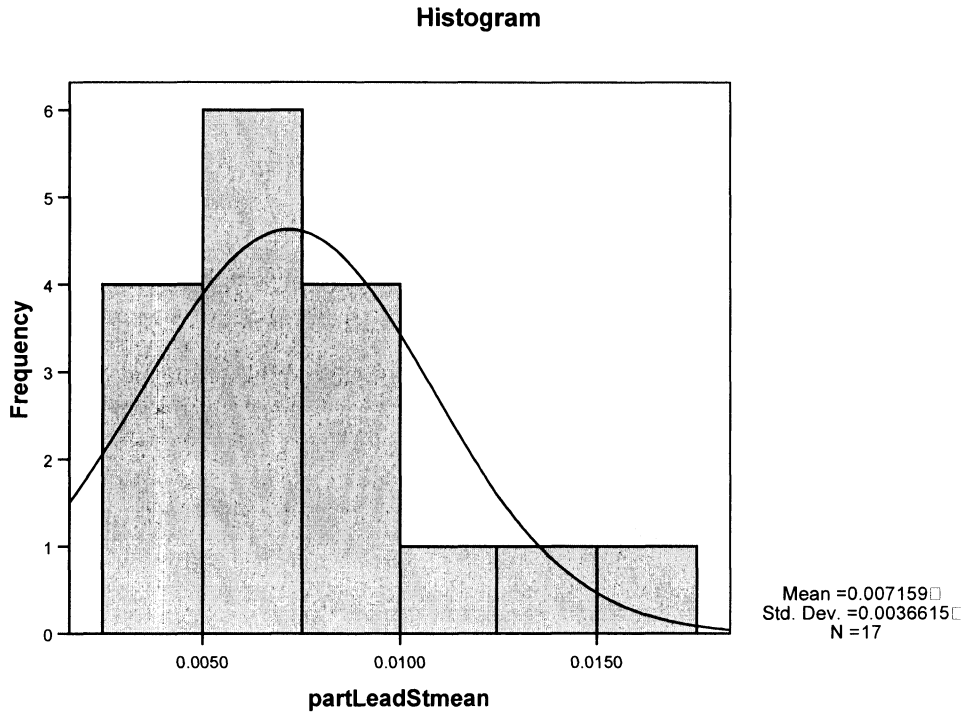


Table 12 and **figure 17** present the data for lead state median concentration in PM for the 18 states with monitoring stations that report to the EPA-AQS. A small absolute range of values that is more widely distributed than was observed with mercury PM is also present that appears more skewed to the right than the mean state lead levels. There was a mean

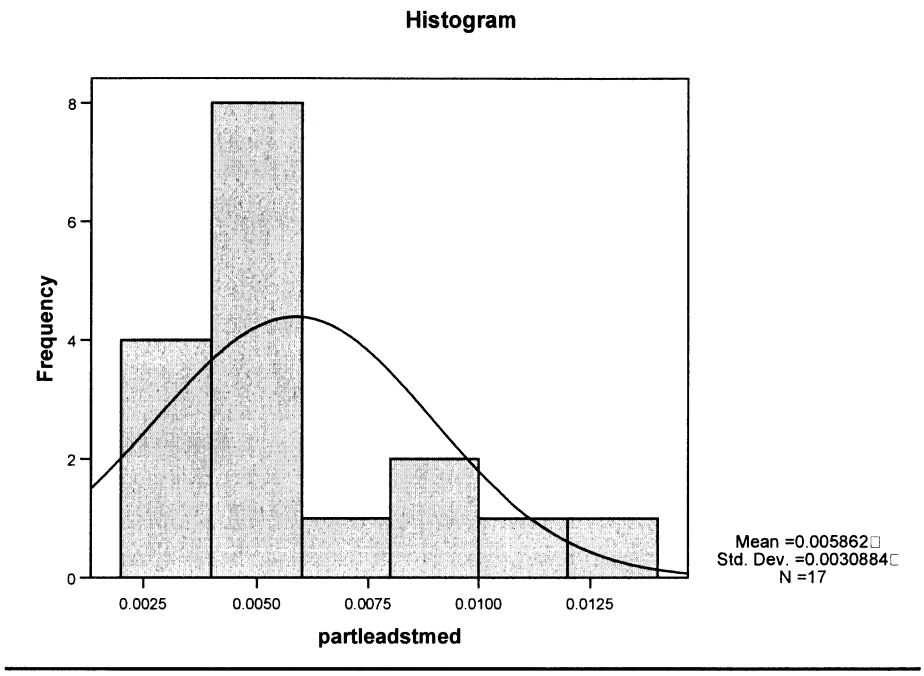
of 0.0059, with a median of 0.0049, and a range from 0.0022-0.0138 by state. The largest number of states were in the 0.0015-0.0085 range (13 states). This also suggests greater variability in PM levels of lead than for mercury. The states that were on the higher end included Michigan and Missouri.

Table 12 Descriptive statistics and frequency distribution for state median lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.

N	Valid	17
	Missing	31
Mean		.005862
Median		.004940
Mode		.0022(a)
Std. Deviation		.003088 4
Variance		.000
Skewness		1.414
Std. Error of Skewness		.550
Kurtosis		1.664
Std. Error of Kurtosis		1.063
Range		.0115
Minimum		.0022
Maximum		.0138

a Multiple modes exist. The smallest value is shown

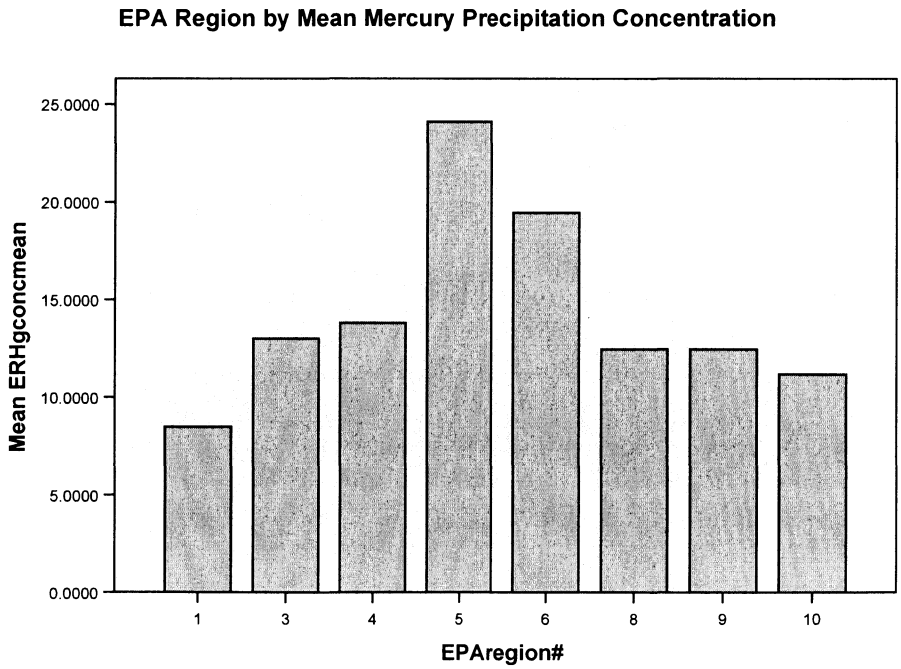
Figure 17 Histogram representing frequency distribution for state median lead particulate matter concentration in 2000 for the 18 states containing monitoring stations that are reporting data to EPA-AQS.



Regions 5 and 6 appears to have the highest values (Figure 18).

Figure 18 Bar chart representing mean mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regions 5 and 6 appears to have the highest values.Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

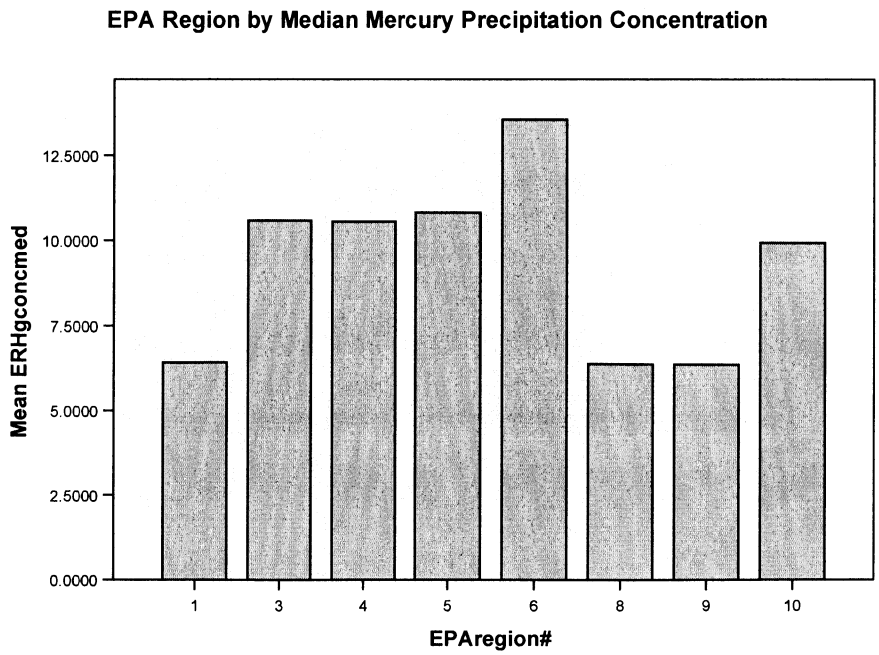
Figure 18 Bar chart representing mean mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regions 5 and 6 appears to have the highest values.



Region 6 appears to have the highest values (Figure 19).

Figure 19 Bar chart representing median mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 6 appears to have the highest values.Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

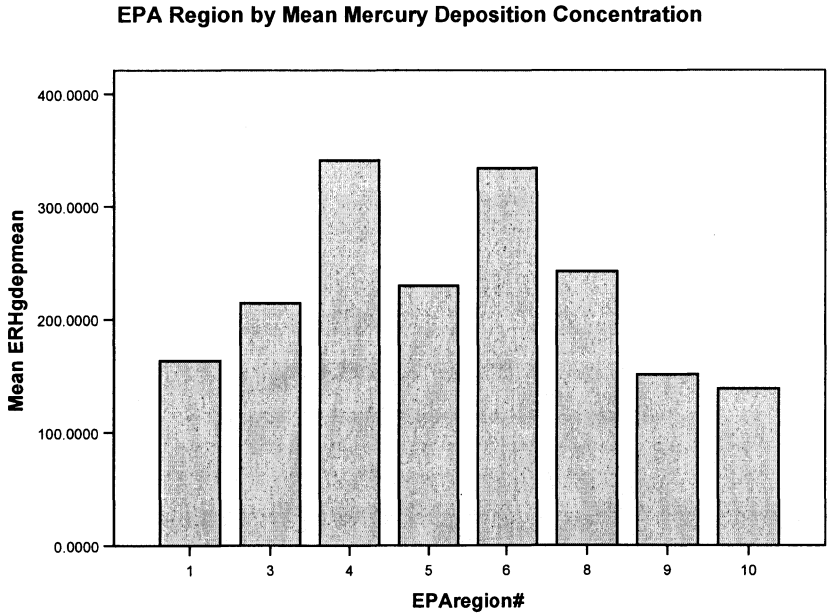
Figure 19 Bar chart representing median mercury precipitation concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 6 appears to have the highest values.



Region 4 and 6 appear to have the highest values (Figure 20).

Figure 20 Bar chart representing mean mercury deposition by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

Region 4 and 6 appear to have the highest values.

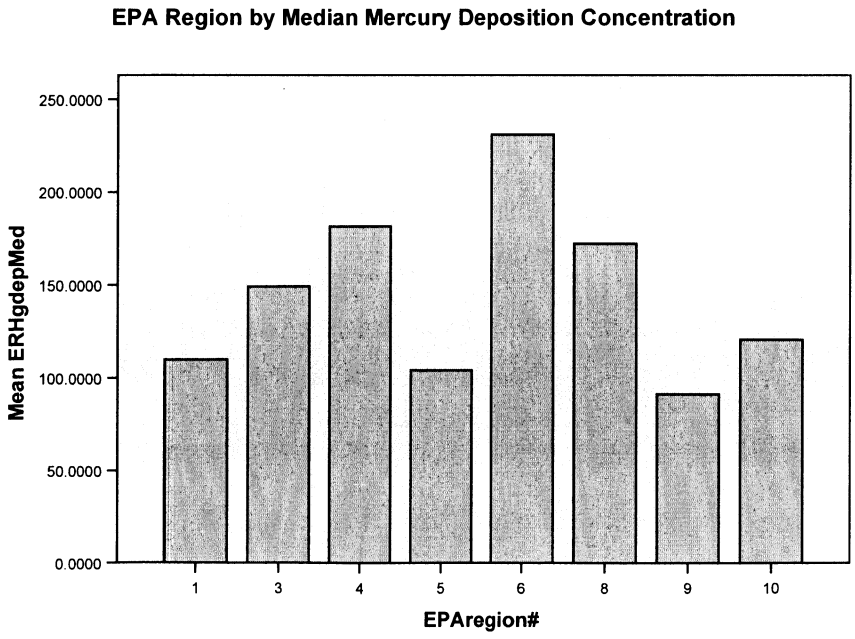


Region 6 appears to have the highest values whereas regions 5 and 9 have the lowest (Figure 21).

Figure 21 Bar chart representing median mercury deposition by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

Region 6 appears to have the highest values whereas regions 5 and 9 have the lowest.

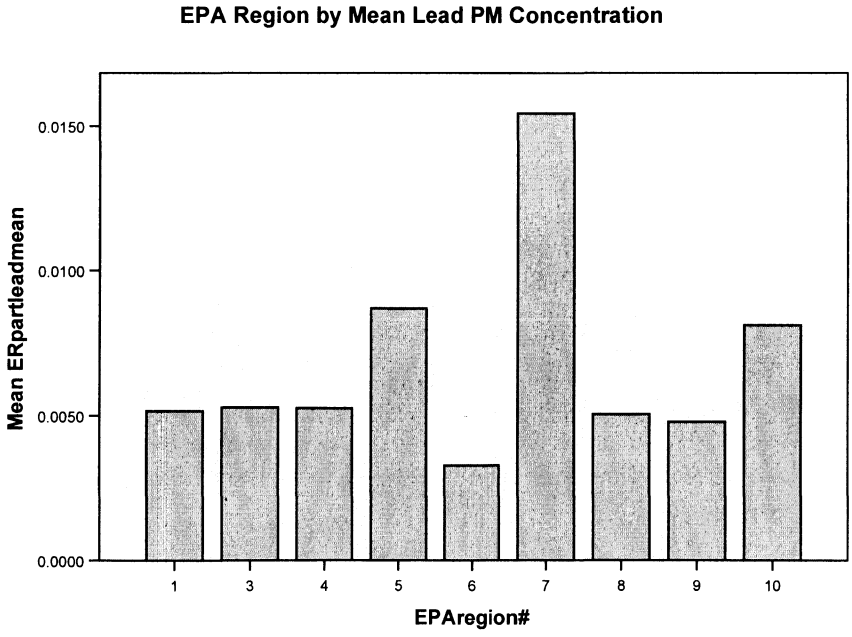
Figure 21 Bar chart representing median mercury deposition by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Region 6 appears to have the highest values whereas regions 5 and 9 have the lowest.



Region 7 appears to have the highest values and region 6 the lowest (Figure 22).

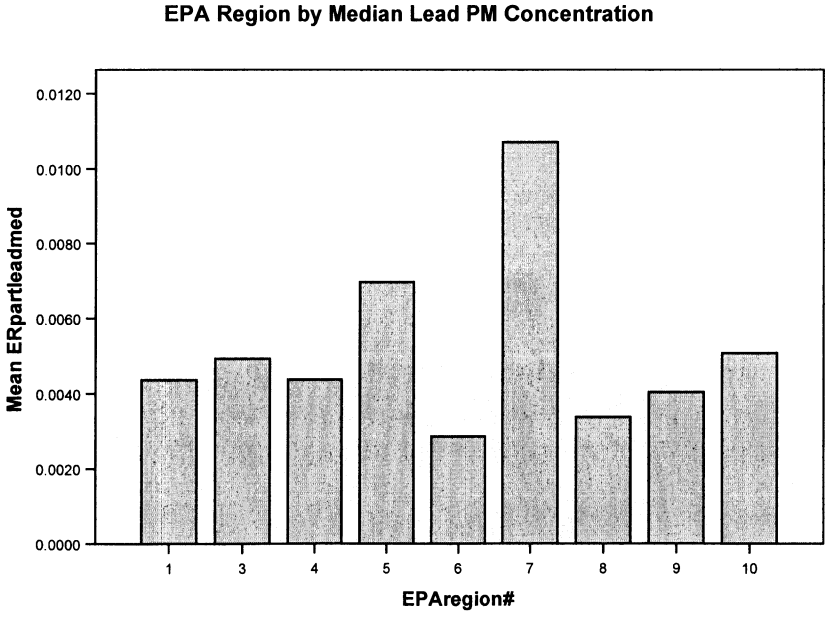
Figure 22 Bar chart representing mean PM lead concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

Region 7 appears to have the highest values and region 6 the lowest.



Similar to the chart above region 7 appears to have highest values and region 6 the lowest (Figure 23).

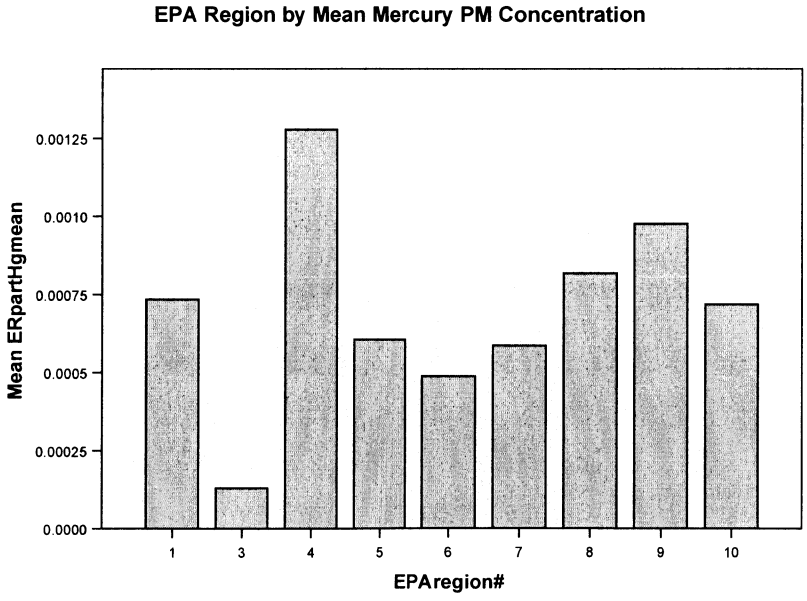
Figure 23 Bar chart representing median PM lead concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.



Region 4 appears to have the highest values and three the lowest (Figure 25).

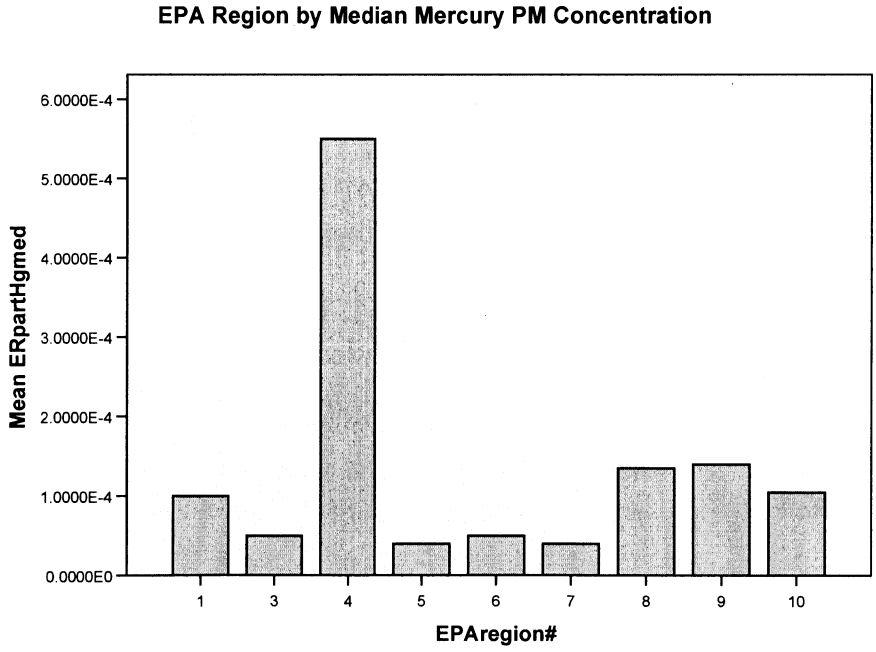
Figure 24 Bar chart representing mean mercury PM concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

Region 4 appears to have the highest values and three the lowests



Region 4 appears to have the highest value as in the previous chart whereas the other regions are much lower (Figure 25).Figure 25 Bar chart representing median mercury PM concentration by EPA region for 3-22 year olds in 2000 for all EPA regions (derived from the collective raw individual exposure levels from all monitoring stations within a region). Regional key: 1(includes1&2) = Northeast, 3 = Mid-Atlantic Coast/Virginias, 4 = Southeast, 5 = Midwest/Great lakes, 6 = South/Southwest, 7 = Midwestern, 8 = Rocky Mountain, 9 = Western/West Coast, 10 = Pacific Northwest.

Again region 4 appears to have the highest value as in the previous chart whereas the other regions are much lower.



Ranking Tables

The following tables rank the states and regions according to either disease rates or exposure levels. This is performed for both mean and median rates and exposure levels. They were sorted according to the disease rates and each of the exposures.

For the states the first column is labeled (Num) for number and is in ascending order. The columns to the right will show the states in ascending order and to their immediate right are the corresponding mean or median disease rates or exposure levels.

The first column for the exposure levels will represent the number of the respective region. These are listed in ascending order with the lowest rate or exposure level at the top and the region with the highest rate or exposure level at the bottom.
Several midwestern states and California rank among the highest for PM for mercury (Table 13).

Table 13 State ranking by order of increasing mean and median particulate matter (PM) for Mercury.

Num	State by Mercury PM (mean)	Mercury PM mcg/m3 (mean)	State by Mercury PM (median)	Mercury PM mcg/m3 (median)
1	michigan	.0000	michigan	.0000
2	pennsylv	.0004	illinois	.0000
3	maryland	.0004	texas	.0000
4	illinois	.0004	utah	.0000
5	texas	.0005	massachu	.0000
6	massachu	.0005	missouri	.0000
7	washingt	.0006	pennsylv	.0001
8	missouri	.0006	washingt	.0001
9	alabama	.0007	alabama	.0001
10	utah	.0008	oregon	.0001
11	oregon	.0009	newyork	.0001
12	northdak	.0009	californ	.0002
13	indiana	.0009	northdak	.0004
14	newyork	.0010	maryland	.0004
15	californ	.0011	florida	.0006
16	florida	.0012	indiana	.0009
17	wisconsi	.0023	wisconsi	.0029
18	ohio	.0043	ohio	.0043

Several midwestern states appear again along with Oregon and are ranked among the highest for lead PM (Table 14).

Table 14 State ranking by order of increasing mean and median particulate matter (PM) for lead. Several midwestern states appear again along with Oregon and are ranked among the highest for PM.

Num	State by Lead PM (mean)	Lead PM mcg/m3 (mean)	State by Lead PM (median)	Lead PM mcg/m3 (median)
1	northdak	.0027	northdak	.0022
2	texas	.0033	texas	.0029
3	arizona	.0041	massachu	.0035
4	massachu	.0041	arizona	.0035
5	maryland	.0051	florida	.0041
6	florida	.0051	utah	.0043
7	californ	.0052	californ	.0045
8	pennsylv	.0053	washingt	.0049
9	newyork	.0060	pennsylv	.0049
10	utah	.0066	maryland	.0051
11	washingt	.0078	newyork	.0053
12	indiana	.0081	oregon	.0054
13	illinois	.0088	illinois	.0072
14	wisconsi	.0090	indiana	.0081
15	oregon	.0106	wisconsi	.0087
16	michigan	.0138	missouri	.0115
17	missouri	.0161	michigan	.0138

Southern and southwestern states appear again and are ranked among the highest which differs from the table 13 for Mercury deposition (Table 15).

Table 15 State ranking by order of increasing mean and median Mercury deposition level.

Num	State by Mercury Deposition (mean)	Mercury Deposition ng/m2 (mean)	State by Mercury Deposition (median)	Mercury Deposition ng/m2 (median)
1	indiana	96.1133	indiana	82.4800
2	washingt	138.8667	californ	91.2050
3	californ	151.4368	wisconsi	91.7000
4	maine	157.7582	maine	104.9350
5	newhamps	160.2343	minnesot	106.6500
6	newyork	186.0668	washingt	120.7250
7	minnesot	214.2099	southcar	120.7900
8	pennsylv	214.4266	newhamps	121.6850
9	illinois	233.2707	illinois	136.8700
10	colorado	242.3000	newyork	140.7300
11	wisconsi	254.8681	pennsylv	149.1000
12	alabama	262.4290	georgia	158.9000
13	georgia	267.7859	colorado	172.1150
14	mississi	270.0281	northcar	182.0400
15	northcar	279.0012	florida	189.7350
16	southcar	311.4513	newmexic	204.3550
17	newmexic	314.2564	louisian	219.8500
18	louisian	319.4276	alabama	227.4450
19	texas	390.6003	mississi	233.0500
20	florida	436.4530	texas	322.7700

A combination of Southern, southwestern and Midwestern states are ranked among the highest which also differs from the table 13 for Mercury precipitation concentration (Table 16).

Table 16 State ranking by order of increasing mean and median Mercury precipitation concentration level. A combination of Southern, southwestern and Midwestern states appear are ranked among the highest which also differs from the table 13 for Mercury PM.

Num	State by Mercury Precipitation Concentration (mean)	Mercury Precipitation Concentration ng/L (mean)	State by Mercury Precipitation Concentration (median)	Mercury Precipitation Concentration ng/m2 (median)
1	indiana	7.8606	newhamps	5.4400
2	maine	8.2120	indiana	5.5450
3	newhamps	8.5300	californ	6.3600
4	newyork	9.5482	newyork	6.4000
5	washingt	11.1726	maine	6.5950
6	northcar	11.4488	northcar	8.5700
7	georgia	11.8756	georgia	9.4650
8	californ	12.4365	colorado	9.7400
9	pennsylv	13.0113	washingt	9.9350
10	colorado	13.4998	wisconsi	10.4600
11	alabama	13.7100	alabama	10.5700
12	mississi	14.2757	pennsylv	10.5750
13	illinois	14.3090	minnesot	10.7900
14	minnesot	14.8524	florida	12.3650
15	southcar	15.1844	mississi	12.5700
16	florida	15.5316	louisian	12.8400
17	louisian	16.7487	texas	13.2950
18	texas	21.5784	illinois	13.3800
19	newmexic	30.2032	southcar	15.6700
20	wisconsi	35.8001	newmexic	27.3300

The states of Minnesota, Oregon, and Maine are ranked among the highest in mean autism prevalence in 3-22 year olds (Table 17).

Table 17 State ranking by order of increasing mean autism prevalence.

Num	State by Autism Prevalence	Prevalence cases/10,000 live births
1	newmexic	14
2	mississi	16
3	colorado	18
4	alabama	24
5	tennesse	25
6	northdak	25
7	louisian	26
8	oklahoma	27
9	nebraska	28
10	iowa	29
11	southdak	29
12	kentucky	29
13	southcar	29
14	wyoming	32
15	kansas	32
16	utah	32
17	montana	33
18	westvirg	34
19	texas	34
20	arizona	35
21	arkansas	36
22	florida	36
23	illinois	36
24	ohio	37
25	delaware	38
26	idaho	41
27	virginia	41
28	missouri	41
29	newyork	42
30	northcar	43
31	georgia	43
32	californ	44
33	washingt	44
34	newhamps	45

35	pennsylv	45
36	michigan	46
37	nevada	48
38	connecti	50
39	rhodeisl	51
40	wisconsi	51
41	massachu	53
42	maryland	55
43	newjerse	56
44	indiana	59
45	vermont	62
46	maine	72
47	oregon	84
48	minnesot	88

The states of Colorado, Missouri, and Arkansas are ranked among the highest in mean autism incidence among three year olds (Table 18).

Table 18 State ranking by order of increasing mean autism incidence in three year olds.

Num	State by Autism Incidence in 3 year olds	Incidence in 3 year olds cases/10,000 live births
1	oklahoma	2.00
2	arkansas	2.10
3	missouri	2.10
4	colorado	2.60
5	mississi	2.70
6	wyoming	3.20
7	newmexic	4.00
8	idaho	4.40
9	ohio	4.80
10	alabama	5.50
11	georgia	6.00
12	virginia	6.40
13	texas	7.20
14	iowa	7.30
15	southcar	7.30
16	southdak	7.70
17	vermont	7.70
18	northdak	7.80
19	utah	7.80
20	nebraska	8.10
21	washingt	8.80
22	kentucky	9.50
23	tennesse	9.90
24	illinois	10.10
25	kansas	10.80
26	louisian	10.90
27	montana	11.00
28	northcar	12.70
29	michigan	13.60
30	indiana	13.80
31	maryland	14.00
32	florida	14.20

33	wisconsi	14.90
34	newhamps	15.70
35	connecti	16.70
36	delaware	19.00
37	nevada	22.40
38	pennsylv	22.60
39	rhodeisl	24.00
40	minnesot	26.50
41	californ	27.90
42	oregon	30.80
43	maine	35.30
44	massachu	38.70
45	oklahoma	2.00
46	arkansas	2.10
47	missouri	2.10
48	colorado	2.60

Table 19 EPA regional ranking by order of increasing mean and median autism prevalence. Regions 1&2, 10, 5, and 3 are ranked among the highest. There is overlap here as well with table 17 on autism prevalence by state.

EPA region by mean prev.	Autism Prev mean	EPA region by median prev.	Autism Prev median
6	27.40	6	27.00
8	28.17	4	29.00
4	30.63	8	30.50
7	32.50	7	30.50
9	42.33	9	44.00
3	46.80	10	44.00
5	52.83	3	45.00
1&2	53.88	5	48.50
10	56.33	1&2	52.00

Table 20 EPA regional ranking by order of increasing mean and median autism incidence among three year olds. Regions 9, 1&2, and 5 are ranked among the highest. There is overlap with table 18 on autism incidence in three year olds by state.

EPA region by Autism incidence 3 yr olds	Mean region autism incidence 3 yr old	EPA region by Autism incidence 3 yr olds	Median region autism incidence 3 yr old
8	27.00	8	6.68
7	29.00	7	7.08
6	30.50	6	8.16
4	30.50	4	8.48
10	44.00	10	11.33
3	44.00	3	15.83
5	45.00	5	22.15
1&2	48.50	1&2	23.02
9	52.00	9	25.15

Table 21 EPA regional ranking by order of increasing mean and median mercury precipitation concentration. Regions 6, 5, 3, and 4 are ranked among the highest.

EPA region by mean mercury precipitation concentration	Mean mercury precipitation concentration ng/L	EPA region by median mercury precipitation concentration	Median mercury precipitation concentration ng/L
7	.	7	.
1&2	8.5000	9	6.3600
10	11.1726	8	6.3600
9	12.4265	1&2	6.4150
8	12.4365	10	9.9350
3	13.0113	4	10.5500
4	13.7932	3	10.5750
6	19.4579	5	10.8150
5	24.1010	6	13.5500

Table 22 EPA regional ranking by order of increasing mean and median mercury deposition concentration. Regions 6, 4, and 8 are ranked among the highest.

EPA region by mean mercury deposition	Mean mercury precipitation deposition ng/m2	EPA region by median mercury deposition	Median mercury deposition ng/L
7	.	7	.
10	138.8667	9	91.2050
9	151.4368	5	104.1300
1&2	163.5126	1&2	110.1100
3	214.4266	10	120.7250
5	229.6449	3	149.1000
8	242.3000	8	172.1150
6	334.0649	4	181.4700
4	341.0803	6	231.1100

Table 23 EPA regional ranking by order of increasing mean and median mercury PM concentration. Regions 4, 9, and 8 are ranked among the highest.

EPA region by mean PM mercury concentration	Mean mercury PM concentration mcg/m3	EPA region by mean PM mercury concentration	Mean mercury PM concentration mcg/m3
3	.0001	7	.0000
6	.0005	5	.0000
7	.0006	3	.0001
5	.0006	6	.0001
10	.0007	1&2	.0001
1&2	.0007	10	.0001
8	.0008	8	.0001
9	.0010	9	.0001
4	.0013	4	.0006

Table 24 EPA regional ranking by order of increasing mean and median lead PM concentration. Regions 10, 5, and 7 are ranked among the highest.

EPA region by mean PM lead concentration	Mean lead PM concentration mcg/m3	EPA region by mean PM lead concentration	Mean lead PM concentration mcg/m3
6	.0033	6	.0029
9	.0048	8	.0034
8	.0051	9	.0041
1	.0052	1	.0044
4	.0053	4	.0044
3	.0053	3	.0049
10	.0081	10	.0051
5	.0087	5	.0070
7	.0154	7	.0107

Discussion and Conclusions

An inherent flaw in ecological studies is drawing cause and effect conclusions about the individual based on aggregated data for the population i.e. the ecological fallacy. However, as the conclusions of such a study may help provide justification for further more detailed analysis, it is difficult to dismiss the importance of these types of studies.

Data Limitations—Autism Data

It is assumed that since the diagnosis and receipt of services depends on medical professional consultation there should not be great variability in defining and identifying children with autism, as the state's discretion would be limited. However, this assumption could not be tested based on the available data, so it remains possible that there is some unknown bias in autism reports. The population that was reported included school-aged children, but 3-22 year olds were included in calculating prevalence. Therefore, the calculated prevalence includes some adults. It should be noted that most cases of autism are manifested, diagnosed and presumably reported within the first years of life on average. The reported incident cases demonstrate a peak around age 5, which probably represents a surge in reporting when children enter the school system (since preschool is not nationally mandated in the same way kindergarten). This trend is observed across all states. A child may have been counted twice due to relocation to another state. However this would likely only be true for the one-year period when the move took place, and would be mostly random. This could have contributed to higher prevalence in states where higher quality services for autistic children are available, for example. This could have influenced the reported incidence as well, since that data is derived directly from the prevalence data, though it probably had a minor effect. The frequency distributions for

autism demonstrated a wide range (see tables 1-3 and graphs 6-8 above, which may further suggest differential reporting in different states).

The registry data provided by Fighting Autism notes that in two studies it was determined that 41%.-66% of community-determined cases were reported into the database. The studies entailed looking at two communities, one in Atlanta, Ga., and the other in Brick Township, N.J. The number of children with autistic spectrum disorder that was listed as their special education designation or recorded as their autism eligibility category was 50-66% and 41% respectively. These percentages represent the fraction of children correctly categorized with autism as their disability on their school record and that were actually reported from the total that should have been reported but due to inaccurate coding in the school record were not reported. This information makes it likely that those children not accurately recorded as autistic in school records would also not be accurately reported as having autism but possibly another disability. (50, 51). Therefore, this supported a trend toward under-reporting. However, clear and consistent trends were seen in all states which show rising prevalence and incidence that is consistent with other published reports. This suggests that despite the under-reporting inherent in many registries, this dataset still demonstrates clear and comprehensive patterns that support rising rates of autism among all states, which gives greater credibility to the dataset despite the flaw in under-reporting. However, a primary concern in this analysis is whether there are differences between states that correlate with measured exposures, and if there is a differential bias in reporting this could affect those correlations artificially in either direction (1,3).

Exposure Data

Another potentially relevant data source for analysis was sentinel animal data. Measurements of environmental toxins (including lead and mercury) have been obtained on a variety of species throughout the country and datasets are available for analyzing these indirect indicators to human exposures. However these datasets were not included, as the focus of this study was on the air quality variable. It was concluded that even if non-migrating species of animals were used, the air conduit hypothesis would not be represented as well by animal data (52).

The major limitation in the exposure datasets included not having monitoring stations for every state, and relying on the states that have them to generate exposure levels for an entire region. This presumes that the exposure levels were uniform and homogeneous throughout the region. The major limitation in the autism disease data-source is the under-reporting and the differential reporting for the various states. The limitation of using modeled data in NATA that is based on emission/release sources, which was discussed earlier, is that the exposure levels are admittedly underestimated per the EPA. The exposure data also has scarcer observations in the earlier years, which makes more recent data better representative of the actual exposure levels over a wider range.

A number of outlying states are also appreciated in many of the datasets (as noted in the above figures 10, 11, 13, 14, and 15) which could suggest clusters of higher exposure levels that warrant further investigation. Again it can be seen that there are wide ranges of

disease rates (14-88) and exposure levels (8-36 in mercury precipitation concentrations) which provide for a wide range of variability in the data that also warrants further exploration. The descriptive statistics and frequency distributions represented by tables 1-11 and figures 7-14 above demonstrate skewed patterns for many of the exposure levels which could be related to using the numerous "0" values that had been recorded in both exposure datasets. Other potential limitations in the data included the presence of solitary 0 values for both the MDN and the PM data (4,5). It was not clear what the '0" values represented. Unlike the missing values they were not dropped and were used for this analysis because it was assumed that they indicated levels below detection (i.e. true 0). However as the databases recorded measurement values to the $10{,}000^{th}$ decimal place their meaning was still in question and would need to be clarified in any future use of the data. They would have to be dropped as well from the datasets produced for this analysis if they in fact represented missing values, as this would preclude their use in this analysis.

A benefit to creating databases for all the years that exposure and disease data are available would be to have a raw data source that could be used to determine if levels of mercury and lead have decreased in the environment. This could be based on using mercury and lead PM and also mercury in precipitation and deposition. Lead levels in air have decreased since the ban on leaded gasoline. However, combustion sources and roadside lead contamination still contribute to lead PM in the air. Mercury has had restrictions placed on emissions in order to reduce ambient levels. This dataset would provide another means to assess the reduction of these toxins in the environment for the years the data is available.

The potential policy implications of this type of ecological research and more detailed individual studies are profound, as they focus on the current standards used to define whether or not current allowable exposure levels are associated with disease. A better appreciation of linkages between heavy metal exposures and disease may also impact on current environmental policy as it relates to the permissible levels of fossil fuel combustion, the principal source of toxic heavy metals in the air. The contribution of toxicity in our population from contamination of important food sources such as fish could possibly be more closely connected to air quality. As sensitivity of detection improves and the sources of exposures are better qualified and described, the actual incidence and prevalence of toxic heavy metal exposure may warrant more urgent action aimed at industrial sources of food contamination. From an occupational health standpoint, many of the current permissible exposure levels, which are already controversial, could also be questioned with respect to air exposure and the potential harm caused by even low levels of exposures in the working population.

Additional potential sources of contamination from poor air quality, such as drinking water, also presents important ramifications as lower air levels of exposure would also reduce bioaccumulation in general including water sources.

These concerns involve the public, media, industry, government leaders, and environmental organizations. These competing interest groups have frequently collided

over the political and policy setting agenda. Further research to investigate and further clarify the risk and appropriateness of current standards appear warranted.

These controversies are not unique to mercury and heavy metals, as the larger issues relate also to other toxic heavy metals, PCB's, or radon gas, etc. This recurring theme of what constitutes safe standards and tolerably safe levels of exposure is not likely to dissipate any time soon. The unknowns concerning the data we have now both from animal testing and from human observational studies has not as yet answered these key questions to our satisfaction. Although we can all agree that heavy metals are known neurotoxins, nephrotoxins, etc., we still cannot definitively show that the current exposure limits, set through standards, are safe in the long term. Does this phenomenon of chronic low-level exposure and subsequent bioaccumulation including total body burden present future health threats in children or adults? The EPA states the following position with respect to this concern: "If you regularly eat types of fish that are high in methyl mercury, it can accumulate in your blood stream over time. Methyl mercury is removed from the body naturally, but it may take over a year for the levels to drop significantly. Thus, it may be present in a woman even before she becomes pregnant. This is the reason why women who are trying to become pregnant should also avoid eating certain types of fish" (11). Our reliance on data for acute toxic levels of exposure is not where this controversy rests. We collectively agree far more on the acute effects than those due to chronic low-level exposure.

Special interests involvement and politics have not given the public reassurance, but have actually fueled the debate and created even further uneasiness. Where does this leave us in formulating sound public health policy? Should we take the position that since science hasn't definitively shown that the current legal standard levels pose a health risk, that we will therefore leave the standards where they currently are set? This is the burden of proof some in industry would have us adopt, especially those likely to incur sizable costs for source reduction and cleanup. Or should we adopt the counter position that there is legitimate concern over the biological plausibility of substances that are clearly poisons presenting a possible future health risk at chronic low-level exposures? Scientific data are currently limited at this time, as is our ability to obtain the type of clear definitive data that would put this issue to rest. Shall we adopt the cautious approach and establish that unless we are definitively shown that the toxins are safe at current levels we will lower them to the lowest detectable levels as has been promoted in other industrialized countries and advocated through the precautionary principle? The choice is whether to set a standard that places the burden of proof in favor of the polluter, even if potential economic threats are exaggerated, or set them in favor of the public's health, when the current standards and data are in question. Past precedent, including court decisions, have compelled the latter even in situations where there was not definitive proof but where the public health establishment had strong compelling arguments in favor of taking such action (such as the Jacobson v. Massachusetts Supreme court decision). The economic argument has been used often in this debate over standards, and it should be noted that we have come from a time before the 1960's, where we had little in the way of regulation and standards, to the present where we have numerous standards and regulations that are

lessening the impact of toxins on our environment and health (53). Yet we remain a potent economic force on the world stage. We have also seen the European Union, another strong economic power with great influence, endorse even more restrictive standards and yet remain economically viable.

We are not likely to answer the key questions with the current methods we have been employing, namely animal data and observational studies, at least not to universal satisfaction. Instead we may be able to shift more research into establishing standards around better biomarkers including peripheral tissue levels in humans i.e. hair, nails, and post chelating agent provocation testing (13, 15, 31, 32,). We can still use observational studies to monitor for health effects of acute exposures as these unfortunate sentinel events are likely to reoccur.

Lastly ecological studies such as that proposed here remain as yet another viable means of studying toxins that cannot be explored in potentially unethical experimental studies,, despite limitations due to ecological fallacy concerns. Ecological studies have the capacity through better design and diligent dataset management to provide useful information, and are a key component to contributing to our knowledge. The expense and logistical challenges in national environmental toxins observational studies result in few studies. Therefore it is reasonable to conclude that ecological studies, based on sound design considerations and comprehensive well managed and diverse datasets, could make national tracking of the effect of exposures on disease rates more valid than is presently accepted or appreciated.

References and Bibliography:

1. FightingAutism Research Education Treatment, Autism Rates. Gibsonia, Pa. Retrieved January 17 2005 from the World Wide Web: http://www.fightingautism.org/idea/index.
2. Department Of Health and Human Services. Centers For Disease Control and Prevention. How Common are Autism Spectrum Disorders. Atlanta Ga. Retrieved February 24, 2005 from the World Wide Web: http://www.cdc.gov/ncbddd/autism/asd_common.htm. Preventing Lead poisoning in Young Children. Retrieved February 24, 2005 from the World Wide Web: http://www.cdc.gov/nceh/lead/publications/PrevLeadPoisoning.pdf.
3. Autism Society of America. Statistics. Retrieved February 24, 2005 from the World Wide Web: http://www.autism-society.org/site/PageServer?pagename=FactsStats.
4. National Atmospheric Deposition Network. Mercury Deposition Network. Champaign, Ill. Retrieved February 24, 2005 from the World Wide Web: http://nadp.sws.uiuc.edu/mdn/.
5. U.S. Department Of Environmental Protection. Air Quality System. Research Triangle Park, N.C. Retrieved March 21, 2005 from the World Wide Web: http://www.epa.gov/ttn/airs/airsaqs/index.htm
6. Visibility Information Exchange Web System. AQS Fine Speciation. Retrieved March 21, 2005 from the World Wide Web: http://vista.cira.colostate.edu/views/

7. Cotran RS, Kumar V, Robbins SL. Cellular Injury and adaptation. In: Cotran RS, Kumar V, Robbins SL. Robbins Pathologic Basis Of Disease. 4th ed., Philadelphia, Pa: W.B. Saunders Company, 1989:1-38.
8. Rubin E, Farber JL, Cell Injury. In: Rubin E, Farber JL, eds. Pathology 1st ed. Philadelphia, Pa.: J.B.Lippincott Company, 1988:2-33.
9. Lewis R, Occupational exposures : Metals. In LaDou J, ed. Current Occupational and Environmental Medicine. 3rd ed. New York, N.Y.McGraw Hill Companies, Inc., 2004:446-9.
10. U.S. department Of Health and Human Servces. Office of Prevention and Health Promotion. Healthy People 2010 Report. Retrieved April 3, 2005 from the World Wide Web: http://www.healthypeople.gov/document/html/tracking/od08.htm#toxicwaste.
11. Public Health Statement For Mercury. Atlanta, Ga. Agency for Toxic substances and Disease Registry Centers for Disease Control and Prevention. March 1999. Retrieved April 24, 2004 from the WWW: http://www.atsdr.cdc.gov/toxprofiles/phs46.html. Top 20 hazardous Substances. April 1999. Retrieved April 24, 2004 from the WWW: http://www.atsdr.cdc.gov/cxcx3.html.
12. Science and Environmental Health Network. Widespread Conference on the Precautionary Principle. Ames, Iowa. Retrieved April 24, 2004 from the WWW: http://www.sehn.org/wing.html.
13. The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR). Bethesda Md. National Institutes if Health,

2004. Retrieved April 17, 2005 from the World Wide Web: http://cerhr.niehs.nih.gov/genpub/topics/mercury.html.

14. Mercury Study Report To Congress: Overview. Washington, D.C.: Environmental Protection Agency. 1997. Retrieved April 17, 2005 from the World Wide Web: http://www.epa.gov/mercury/reportover.htm.
15. What you need to know about mercury in fish and shellfish. 2004 EPA and FDA Advice For: Women who might become pregnant, Women who are pregnant, Nursing mothers, Young children. Washington D.C.: Food and Drug Administration Retrieved April 17, 2005 from the World Wide Web: http://www.cfsan.fda.gov/~dms/admehg3.html.
16. ADA Positions and Statements ADA Statement On Dental Amalgam. Chicago, Ill.: American Dental Association, 2002. Retrieved April 17, 2005 from the World Wide Web: http://www.ada.org/prof/resources/positions/statements/amalgam.asp.
17. Siblerud RL, Kienholz, E. Evidence that mercury from silver dental fillings may be an etiologic factor in multiple sclerosis. Science of the Total Environment 1994;142:191-205.
18. Langauer-Lewowicka H, Zajac-Nedza M. Changes in the nervous system due to occupational metallic mercury poisoning. Neurologia I Neurochirurgia Polska 1997;31:905-13.
19. Adams CR, Ziegler DK, Lin JT. Mercury intoxication simulating amyotrophic lateral sclerosis. [Polish] JAMA 1983;250:642-3.
20. Felmus MT, Patten BM, Swanke L. Antecedent Events in amyotrophic lateral sclerosis. Neurology 1976;26:167-72.

21. Mano Y, Takayanagi T, Ishitani A, Hirota T. Mercury in hair of patients with ALS. [Japanese] Rinsho Shinkeigaku – Clinical Neurology 1989;29:844-8.

22. Mano Y, Takayanagi T, Abe T, Takizzawa Y. Amyotrophic lateral sclerosis and mercury-preliminary report. [Japanese] Rinsho Shinkeigaku – Clinical Neurology 1990;30:1275-7.

23. Moriwaka F, Tashiro K, Doi R, Satoh H, Fukuchi Y. A clinical evaluation of the inorganic mercurialism – its pathogenic relation to amyotrophic lateral sclerosis. [Japanese] Rinsho Shinkeigaku – Clinical Neurology 1991;31:885-7.

24. Vanacore N, Corsi L, Fabrizio E, Bonifati V, Meco G. Relationship between exposure to environmental toxins and motor neuron disease. [Italian] Medicina del Lavoro 1995;86:522-33.

25. Louwerse ES, Buchet JP, Van Dijk MA, de Jong VJ, Lauwerys RR. Urinary excretion of lead and mercury after oral administration of meso-2,3-dimercaptosuccinicacid in patients with motor neuron disease. International Archives of Occupational & Environmental Health 1995;67:135-8.

26. Bernard SE, Redwood A, Roger H, Binstock, T. Autism a novel form of Mercury Poisoning. Medical Hypothesis 2001;56:462-71.

27. Holmes ASB, Reduced levels of mercury in first baby haircuts of autistic children. International Journal of Toxicology 2003;22:277-85.

28. Geier DA, Geier MR. A comparison evaluation of the effects of MMR immunization and mercury doses from thimersol-containing childhood vaccines on the population prevalence of autism. Medical Science Monitor 2004;10:33-39.

29. List of drinking Water Contaminants and MCL's: National Primary Drinking Water Regulations. Washington D.C.: Environmental Protection Agency, 2005. Retrieved April 17, 2005 from the World Wide Web: http://www.epa.gov/safewater/mcl.html

30. Mercury Toxfacts. Atlanta, Ga. Agency For Toxic substances and Disease Registry Centers for Disease Control and Prevention. April 1999. Retrieved April 24, 2004 from the WWW: http://www.atsdr.cdc.gov/tfacts46.html

31. Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Zhaofa X, Hurlbut KM, Aphosian MM, et al. Sodium 2,3-Dimercaptopropane sulfonate Test for mercury in humans.III. Urinary Mercury after exposure to mercurous chloride. The Journal of Pharmacology and Experimental Therapeutics 1996;277:938-44.

32. Aposhian HV, Maiorino RM, Gonzalez-Ramirez D, Zuniga-Charles M, Zhaofa X, Hurlbut KM, et al. Mobilization of heavy metals by newer, therapeutically useful chelating agents. Toxicology 1995;97:23-38.

33. Antidotes. In: Kenneth HK, Kastrup EK, eds. Drug Facts and Comparison. 57th ed., St. Louis, Mo.:Walters Klauer Co., 2003:441-443.

34. Knuckles M, Welford RC, Toxicology. In: Morgan TM, ed. Environmental Health. 3rd ed. Belmont, Ca.: Wadsworth/Thomson Learning, 2003: 151-60.

35. Feldman RG, Chang-Ming JC. Neurotoxic disorders. In: McCunney RJ. A Practical Approach to Occupational and Environmental Medicine. 3rd ed., Philadelphia, Pa.: Lippincott Williams & Wilkins, 2003:374-5.

36. Harber P, Conlin C, McCunney RJ. Occupational Medical Surveillance. In: McCunney RJ. A Practical Approach to Occupational and Environmental Medicine. 3rd ed., Philadelphia, Pa.: Lippincott Williams & Wilkins, 2003:591.

37. U.S Environmental Protection Agency. Regions. Research Triangle, N.C. Retrieved April 2, 2006 from the WWW: http://www.epa.gov/epahome/locate2.htm.

38. Population reference Bureau. Lesson Plan: People on the Move. Activity One: Moving On: Population Mobility in the United States. Washington, D.C. Retrieved March 16, 2006 from the WWW: http://www.prb.org/Content/NavigationMenu/PRB/Educators/LessonPlans/People_on_the_Move/Moving_On%E2%80%94Population_Mobility_in_the_United_States.htm .

39. Population reference Bureau. Lesson Plan: People on the Move. Activity One: Moving On: Population Mobility in the United States. Washington, D.C. Retrieved March 16, 2006 from the WWW: http://www.prb.org/Content/NavigationMenu/PRB/Educators/LessonPlans/People_on_the_Move/Population_Mobility_is_Changing_My_State.htm .

40. National Atmospheric and Oceanic Administration. Jet Stream An online Weather School. Origin of Wind. Retrieved April 18, 2006 from the WWW: http://www.srh.noaa.gov/srh/jetstream/synoptic/wind.htm.

41. Public Interest Research group in Michigan. Michigan Joins Lawsuit Challenging EPA Mercury Rule Action is Consistent with Granholm's Promise to Reduce

Mercury in Michigan. 2005. Retrieved April 18, 2006 from the WWW: http://pirgim.org/MI.asp?id2=18649.

42. National Resource Council of Maine. Augusta Me. 2004. Retrieved April 18, 2006 from the WWW: http://72.14.203.104/search?q=cache:Ptt3-BN0gT0J:nrcm.org/merc2/merc_levels_kj0804.htm+%22coal+burning+states%22&hl=en&gl=us&ct=clnk&cd=5
43. U.S Environmental Protection Agency. National Air Toxics Assessment. Research Triangle, N.C. Retrieved April 2, 2006 from the WWW: http://www.epa.gov/ttn/atw/nata/index.html.
44. U.S Environmental Protection Agency. National Air Toxics Assessment FAQ. Research Triangle, N.C. Retrieved April 2, 2006 from the WWW: http://www.epa.gov/ttn/atw/nata/natsafaq.html#B10.
45. Northeastern States for coordinated Air Use Management. Regional Air Quality Monitoring Program. Boston, Ma. Retrieved April 2, 2006 from the WWW: http://www.nescaum.org/about-us/contact-information.
46. University of Adelaide. Department of Chemistry. Spectroscopy. Retrieved March 1, 2006 from the WWW: http://www.chemistry.adelaide.edu.au/external/soc-rel/content/ac-meths.htm.
47. Microsoft Excel Spreadsheet Application, Microsoft Corporation Inc. Redmond, Washington. 2003.
48. Van Hoesen KB, Clark, RF. Seafood Toxidromes. In: Auerbach P, ed. 4th ed. St. Louis, Missouri: Mosby Inc., 2001: 1316.
49. SPSS Statistical Software. Version 14. 2006. SPSS Inc. Chicago, Ill.

50. Yeargin-Allsopp M, Rice C, Karapurkan T. Prevalence of Autism in a U.S. Metropolitan Area. JAMA 2003;289:49-55.

51. Bertrand J, Mars A, Boyle C. Prevalence of Autism in a U.S. Population: the Brick Township, New Jersey Investigation. Pediatrics 2001;108:1155-61.

52. Kamman NC, Burgess NM, Driscoll CT, et. al. Mercury in Freshwater Fish of Northeast North America – A Geographic Perspective Based on Fish Tissue Monitoring Databases. Ecotoxicology.

53. Morgan, MT, Summary of Environmental Laws. In: MT Morgan, Environmental Health 3rd ed. Belmont, Ca. Thomson Wadsworth, 2003:319-328.

54. U.S. Department of special Education. Office of Special Education Projects. Individuals with Disabilities Education Act. Retrieved March 1, 2006 from the WWW: http://www.nectac.org/~pdfs/idea/OSEPeci.PDF.

55. Blaxill MF, What's Going On? The Question of Time Trends in Autism, Public Health Reports, Nov-Dec 2004, Vol 119.

56. Jyonouchi H Geng L, Ruby A. Dysregulated innate immune responses in young children with autim spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. Neuropsychobiology. 2005;51(2):77-85.

57. Jyonouchi H, Sun S, Itokazu N. Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. Neuropsychobiology. 2002;46(2):76-84.

58. Treatment of autism spectrum disorder children with thiamine tetrahydrofurfuryl disulfide: a pilot study. Neuroendocrinolohy Letter 2002 Aug;23(4) 303-8.